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VCM
20

Annotations

917 Management of infantile gastroenteritis *J A Walker-Smith*
919 Use of hearing aids in infancy *Sally Wood, Barry McCormick*
921 Phenobarbitone and febrile convulsions *D P Addy*

Original articles

922 Magnetic resonance imaging in neurological disorders *Alun C Elias-Jones, Timothy Jaspan, David H Mellor, et al*
930 Slow release carbamazepine in treatment of poorly controlled seizures *S W Ryan, I Forsythe, R Hartley, et al*
936 Acute gastroenteritis in infants under 6 months old *R Fox, C L S Leen, E M Dunbar, et al*
939 Management of gastroenteritis *H R Jenkins, B M Ansari*
942 Prognosis of chronic granulomatous disease *A Finn, N Hadžić, G Morgan, et al*
946 Latent sensitisation to respiratory syncytial virus during acute bronchiolitis and lung function after recovery *S J Caswell, A H Thomson, S P Ashmore, et al*
953 Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death *D P Southall, M P Samuels, D G Talbert*
962 Carpal tunnel syndrome in the mucopolysaccharidoses and related disorders *J E Wraith, S M Alani*
964 Natural and modified history of complete atrioventricular septal defect—a 17 year study *P Frontera-Izquierdo, G Cabezuelo-Huerta*
968 How curable is relapsed Wilms' tumour? *J J Groot-Loonen, C R Pinkerton, P H Morris-Jones, et al*
971 Pharmacokinetics of paracetamol after cardiac surgery *C S Hopkins, S Underhill, P D Booker*
977 Plasma prolactin and clinical outcome in preterm infants *A Lucas, B A Baker, T J Cole*
984 Social integration of the older thalassaemic patient *C Politis, A Di Palma, M Fisfis, et al*
987 The iris in Williams syndrome *G Holmström, G Almond, K Temple, et al*
990 Perforated duodenal ulcer: an unusual complication of gastroenteritis *Jane M Wilson, Christopher R Darby*
991 An unusual cause of thoracic mass *D C Wilson, A O B Redmond*
992 Spontaneous resolution of congenital nephrotic syndrome in a neonate *G R Banton, B Thalayasingam, M G Coulthard*
994 Congenital diaphragmatic hernia: impact of prostanoids in the perioperative period *A P Bos, D Tibboel, F W J Hazebroek, et al*

Current topic

996 Reflux vomiting *P J Milla*

Personal practice

1000 Psychological guidelines in the management of paediatric organ transplantation *Roger Bradford, Laura Tomlinson*

Medical education

1004 Examinations in paediatric training *Graham S Clayden*

Personal paper

1009 Senior house officer posts in community paediatrics—an introduction to child health *Jan Welbury, Arthur Paynter, J M Parkin*
1011 **Sister journals—the Soviet Union** *R H D Boyd*
1012 **Letters to the editor**

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Annotations

Management of infantile gastroenteritis

There has been a dramatic fall in the mortality from acute gastroenteritis in childhood in developed countries. In western Europe mortality statistics from acute diarrhoea have fallen to zero for some countries such as the Netherlands in 1984. In the United Kingdom the mortality was zero in Northern Ireland in 1983, 1984, and 1985 (World Health Organisation regional statistics). For England and Wales there has been a dramatic fall in annual mortality in recent years from about 300 in the late 1970s, to about 25 in the late 1980s. Nevertheless, there are still too many children dying each year. Furthermore, as the study of Conway *et al* in Leeds makes clear, gastroenteritis continues to be a significant cause of paediatric morbidity in Britain especially in infants from socially disadvantaged families.[1]

This recent fall in mortality is related to the dramatic reduction in the incidence of hypernatraemic dehydration and consequent death from this cause.[2] The earlier much more significant fall in mortality from the appalling mortality levels at the beginning of this century, when about 30–50 000 children died in England and Wales each year, relate to the improvement in public health and personal hygiene. These dramatic falls in mortality in Western countries occurred well before the widespread use of modern oral rehydration therapy, which has done so much to reduce mortality in the developing world in recent years.

Nevertheless, the most important part of modern management of infantile gastroenteritis centres upon appropriate oral rehydration therapy. This is generally agreed in principle, although the details—that is, the most appropriate sodium concentrations and carbohydrate content—remain matters for discussion at least in the developed countries.[3-5] It is depressing to find out, however, that only 30·8% of infants had been given oral rehydration therapy in the study of Conway *et al* particularly as over 60% had visited their general practitioner.[1] Clearly more education is required in this country for doctors as well as parents of children.

A policy for refeeding babies after gastroenteritis and the need for special formula feeding after gastroenteritis in infancy, remain more controversial issues. There is less general agreement in this area.

It has been the practice in the United Kingdom for some years for children with acute gastroenteritis after 24 hours of oral glucose electrolyte solution to reintroduce gradually the infant's usual feeds by a system known as regarding. In recent years the need for this approach for infants over the age of 6 months has been questioned and the practice of regrading in this age group has largely been abandoned. More caution has been used for infants less than 6 months of age.[6] There are now studies to indicate that even in this age group, however, immediate return to the infant's formula feed is to be recommended as routine practice.[7 8]

This is a more important issue in developing countries where malnutrition is common and any prolonged reduction of energy intake after gastroenteritis must be avoided. Certainly the continuation of breast feeding throughout the episode of diarrhoea supplemented by oral rehydration therapy is recommended for breast fed babies whether they be in developed or developing communities.[9]

Why was regrading so popular for so long? This may relate to the high incidence of lactose intolerance as a complication of acute gastroenteritis in the past, whereas lactose intolerance now appears to be declining as an important problem according to most reports.[10] Fox *et al*, however, did not find any difference in lactose intolerance between a regraded group and a non-regraded group of infants with gastroenteritis, yet their overall incidence of lactose intolerance was high.[8] Their series was rather atypical, however, as the incidence of rotavirus was so low and the finding of other pathogens so high. Were they describing cases of cows' milk protein intolerance, complicated by gastroenteritis presenting as lactose intolerance?

When considering a policy for refeeding after gastroenteritis for bottle fed infants, the relative importance of cows' milk intolerance either as lactose intolerance or cows' milk allergy, as a complication of acute gastroenteritis must be assessed in each individual community concerned. Its relative frequency, and so importance, varies widely from centre to centre and currently apart from the report of Fox *et al* appears to be in decline in the United Kingdom, Northern Europe, and North America.[10]

Cows' milk intolerance may be due to cows' milk allergy or lactose intolerance, or both, as occurs in some cases of cows' milk sensitive enteropathy. Indeed cows' milk allergy can present as lactose intolerance.

In these northern communities, because of improvement in modern adapted milks making formulas less sensitising, cows' milk allergy as a complication of gastroenteritis, appears to be a declining problem. As a result, the traditional approach of regrading for patients with gastroenteritis no longer seems necessary. Furthermore, as cows' milk intolerance—whether it be lactose intolerance or cows' milk allergy—is no longer such an important problem as a complication of gastroenteritis as it was formerly, therefore a prophylactic lactose free formula is not routinely indicated. Indeed although lactose free soy formulas have been recommended for routine use after gastroenteritis,[8] there is a risk of developing soy sensitive enteropathy.[11] [12] There are indeed a number of foods that may damage the small intestinal mucosa when fed in early infancy especially to infants who already have cows' milk sensitive enteropathy.[13] It thus does seem unwise to feed new foods at this time of small intestinal mucosal vulnerability.

The diagnosis of lactose intolerance in these circumstances is usually based upon the presence of 1% or more stool reducing substances; Fox *et al* make the diagnosis when 0·5% or more reducing substances are found.[8] This could explain their higher incidence than that reported in recent years, although patient selection is certainly possible. No child in their series had recurrence of diarrhoea seven days after refeeding, which shows that lactose intolerance occurred only during the time of the acute infection. Fox *et al* recommended an immediate change of feed to a lactose free feed (for example, Wysoy (Wyeth)) when lactose intolerance was diagnosed. An alternative strategy is to return for 24 hours to an oral rehydration solution and then regrade back onto cows' milk formula.[14] In this way the need for a special formula is avoided. Lactose intolerance in this circumstance is likely to be very brief in duration as it merely reflects the presence of gastrointestinal infection causing temporary change to the small intestinal mucosa.

When diarrhoea on cows' milk feeding persists for more than two weeks after the onset of diarrhoea, then the cause of this chronic diarrhoea should be sought. Investigation should include stool microbiology to detect nosocomial infection or persistent stool pathogens such as enteropathogenic *Escherichia coli*, *Giardia lamblia*, or cryptosporidia. Small intestinal biopsy should be considered in these circumstances to diagnose the presence of enteropathy. When specific pathogens are excluded the most likely cause is a temporary cows' milk sensitive enteropathy. Then a cows' milk free formula should be prescribed. A protein hydrolysate is recommended.

Conclusions

While breast feeding is ideal for infants, in those who are bottle fed the morbidity from acute gastroenteritis should be reduced by continuing to feed babies with a formula of low sensitising capacity after a relatively period of an oral rehydration solution. This both ensures adequate energy intake and reduces the risks of developing postenteritis milk intolerance.

Cows' milk protein intolerance is a relatively uncommon complication occurring in only 2·9% of the large series of 1148 children reported by Conway *et al.*[1] Interestingly Conway *et al* do not mention lactose intolerance per se in their report.[1] They probably include it within the term cows' milk protein intolerance as they define it. Clearly there is a real need to describe accurately the relative importance of milk intolerance either as cows' milk allergy or lactose intolerance in bottle fed infants who develop gastroenteritis in individual communities.

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See related articles on p 936 and p 939.

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Archives of Disease in Childhood 1990; **65**: 919–920

Use of hearing aids in infancy

Congenital sensorineural hearing loss often remains undetected until the second or third year of a child's life.[1] With recent improvements in screening techniques and the advent of neonatal screening programmes we expect to detect infants with severe and profound hearing loss within the first year of life and to see a significant number under the age of 6 months. It is widely accepted that the earlier the habilitation of a child with a severe or profound hearing loss starts, the better the outcome is likely to be. Markides has demonstrated better speech intelligibility in children who were fitted with amplification in their first six months of life compared with children fitted after this age.[2] Selection and use of amplification is a part of this habilitative process.

The first problem in the selection of appropriate amplification lies in obtaining sufficient and accurate information about the child's hearing sensitivity over the essential speech frequency range—that is, 500–4000 Hz. Once the infant reaches the age of 6 months or so and is sitting independently with good head control it is usually possible to obtain reliable information about hearing sensitivity using distraction or visual reinforcement audiometric techniques. In an infant whose developmental problems preclude this form of testing, and in infants under the age of 6 months, electric response audiometry is usually required in order to obtain reliable threshold information. The auditory brainstem response is usually the choice for threshold determination in infants. This gives threshold information about high frequency hearing but not low frequency hearing and this is one of its limitations.[3] To obtain information about the low frequency hearing it is essential to carry out careful observation of the child's responses to auditory stimuli in the sound field. The initial selection of amplification characteristics and fitting of hearing aids is usually based, of necessity, on rather limited information, particularly in the infant under 6 months of age. The child is monitored closely initially: parents' and teachers' observations are noted and audiological testing of the infant is carried out both with and without hearing aids. In this way a more detailed audiological picture is obtained and changes to the hearing aid prescription made as required.

Amplification is usually recommended for hearing losses greater than 30 dB averaged across the speech frequency range in the better ear. This, however, is only a guideline, and the individual's needs must be taken into consideration. For example, a child with a lesser degree of hearing loss but with an appreciable speech delay may well benefit from amplification whereas another child may cope adequately with a slightly greater degree of loss. In fitting hearing aids in infants we are usually dealing with more severe losses where amplification is clearly indicated. The difficulties associated with measuring mild losses accurately in infants and in convincing parents that there is a problem usually preclude fitting infants with mild degrees of hearing loss unless there is a clear and demonstrable high frequency hearing loss.

The aim in providing amplification is to make as much speech information as possible available by amplifying speech to fit within the listener's dynamic range of hearing. The dynamic range is the range between the threshold of hearing and the level at which sound becomes uncomfortable—the loudness discomfort level. The more severe the hearing loss, the more limited the amount of speech information that can be made available. Hearing aid selection involves choosing the electroacoustic characteristics of the hearing aid (gain, frequency response, and maximum output) in order to achieve the above. The way in which these characteristics should be chosen has been the subject of much research and publication over the years and a number of prescriptive techniques have been put forward.[4–6]

Whatever method of selection is used it is necessary to evaluate the hearing aid fitting and one method is to obtain aided sound field thresholds (using warble tone or narrow band noise stimuli) when the infant is wearing the hearing aids. This gives a measure of the amount of speech frequency information that is available to the child. It is important to avoid excessively high levels of amplification that will prove uncomfortable and lead to the child rejecting the hearing aid, but it is equally important to ensure that enough amplification is being used.

The potential of high levels of sound to damage hearing is well known. Naturally there is concern about the potential of high output levels produced by present day hearing aids to further damage the users residual hearing. This has been the subject of a number of surveys,[7] but no conclusive evidence has been produced. Any possible risk must be weighed against the disadvantage to the child in not utilising residual hearing to the full.

Hearing aids

Hearing aids are generally relatively unsophisticated devices, although advanced signal processing systems are being developed. At present most are basically amplifiers with some facility to (i) manipulate the relative amount of amplification at different frequencies, (ii) control the maximum output, and (iii) selectively alter the gain in order to 'compress' a wide range of sounds to fit within the user's dynamic range. A hearing aid basically consists of a microphone that converts the incoming sound to an electrical signal, an amplifier with a variable gain control, and a receiver that converts the amplified electrical signal back into an acoustic signal. The power supply is provided by a battery.

In postaural aids all these components are housed in one case, which is worn behind the ear. The aid is coupled to the earmould, which is individually made for the infant's ear, via a small elbow or hook on the hearing aid. This is connected to the tubing that provides a channel through the earmould and delivers the amplified acoustic signal deep into the meatus of the ear.

In the ear aids, where all the components are mounted in an earmould that fits into the canal and concha of the external ear, are now available. These aids are generally not suitable for growing infants because of the cost of frequent replacement of the system caused by growing ears.

With body worn hearing aids, the microphone, amplifier, and batteries are contained in a unit that is mounted on the child's chest, usually in some sort of harness. The receiver is external and is connected via a lead to the body worn unit. The receiver itself clips directly into the earmould and is held there by a retaining spring clip.

All of these types of aid described so far (postaural, in the ear, and body worn) deliver the acoustic signal via air conduction deep into the external meatus of the ear and the resulting acoustic signal is transmitted via the middle ear to the cochlea and beyond in the normal way. It is also possible to use a bone conduction hearing aid. In this case the receiver consists of a head worn vibrator (rather like the bone conductor on an audiometer), which is worn on the mastoid process and delivers an acoustic signal to the cochlea by vibration of the skull and soft tissue. The remaining components may be mounted in either a postaural or a body worn unit. These aids are only used when there is no alternative—in cases of atresia, where the normal air conduction route is not available, or sometimes in cases of chronically discharging ears where the condition is aggravated by the presence of an earmould. This type of aid is difficult to use and retain with young children. Recent developments in the area of implanted bone conduction aids show great promise for children with problems such as bilateral atresia.[8]

For the vast majority of young children the choice is between a postaural or body worn instrument. There is little to choose between the two in terms of technical performance and postaural aids will be the usual option. The only exception to this is children with low frequency residual hearing only (with so called left hand corner audiograms) where body worn aids may be considered. With the range of smaller postaural aids now available it is usually possible to fit the smallest ears. It may be necessary to use minihooks on hearing aids, double sided adhesive discs which secure the aid to the side of the head, special clips attached to the aid, or plastic retaining devices to help maintain the aid in position. The consensus regarding binaural fitting (one aid for each ear) is that this should be done routinely unless there is a good reason not to. There are a number of advantages in binaural as opposed to monaural fitting including enhanced sound localistation ability and the achievement of higher signal levels because of the binaural summation effect.[9]

One of the problems with hearing aid use is the poor signal:noise ratio which occurs when all acoustic stimuli arriving at the microphone of the aid are amplified. One way of overcoming this is by the use of remote microphone systems, for example in the use of radio systems. These are commonly used by hearing impaired children in educational settings and by some preschool children at home. The mother or teacher wears a transmitter that picks up her voice and transmits it by radio frequency to a receiver worn by the child. In this way the problems of distance between speaker and listener and of background noise can be overcome to some extent and a better signal:noise ratio achieved. Evans discusses hearing aid systems more fully.[10]

Ear moulds

The earmould is an integral part of the amplication system. Its function is to deliver the amplified sound from the hearing aid receiver into the ear canal. It also serves to retain a postaural aid in position behind the ear or the receiver of a body worn hearing aid in the ear. In order to do this an earmould must be manufactured from appropriate material so that it is comfortable to wear for all of a child's waking hours and is capable providing an extremely good acoustic seal. The need for the former is obvious if a child is to accept hearing aids; the latter requirement is particularly important when high levels of gain and output are required as in cases of severe and profound hearing loss. Failure to provide a good acoustic seal results in acoustic 'feedback'—a characteristic high pitched whistle that arises when amplified sound escapes around a poorly fitting earmould and is picked up by the microphone of the hearing aid and reamplified. The better the acoustic seal provided by the earmould the less the likelihood of this type of feedback occurring. There are other causes of feedback that may also need to be considered.[11]

The problems associated with the provision of good earmoulds for children are well known and have been the subject of a number of surveys.[12] With a skilled impression taker using a standard technique, however,[13] and the availability of suitable earmould materials, good earmoulds can be provided. It is essential that earmoulds for children are made of soft materials—for example, soft acrylic, silicone, or molloplast in order to satisfy the requirements of comfort and a good acoustic seal. In the case of rapidly growing infants, who require extremely well fitting earmoulds in order to deliver the required gain levels, it may be necessary to renew earmoulds as frequently as every three or four weeks.

Management of the hearing impaired infant

This requires a team approach to deal with the needs of the infant and family. In addition to the audiological aspects involved in the measurement of hearing sensitivity and the selection, provision, and monitoring of amplification there are more specifically medical and educational needs. The infant will be seen by a consultant in otolaryngology or audiological medicine to assess whether there is any possible medically or surgically correctable cause of the hearing loss, or part of it, and to authorise the fitting of hearing aids. In addition, the child should be seen for a full developmental assessment including assessment of visual problems and for investigations into the aetiology of the hearing loss with referral for genetic counselling where appropriate. Hearing impaired infants and their families also require educational and rehabilitative support. In most areas infants with a permanent hearing loss and fitted with hearing aids would expect to receive regular home visits from a specialist teacher of the deaf whose role is to provide guidance and support to the family as a whole, rather than having a very specific teaching role, as well as maintaining an overview of the child's progress. Increasingly specialist speech therapists with additional qualifications in working with the hearing impaired are also involved in this area. Close liaison between all these professionals and the family is essential. It is also important to inform families about relevant voluntary organisations that can provide help and support.

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Archives of Disease in Childhood 1990; **65**: 921

Phenobarbitone and febrile convulsions

The value of long term anticonvulsant prophylaxis in children who have had febrile convulsions has been debated for many years. In a recent paper in the *New England Journal of Medicine*, Farwell *et al* concluded that phenobarbitone depresses cognitive performance without preventing seizure recurrence.[1] After two years the mean intelligence quotient in children assigned to phenobarbitone treatment was 8·4 points lower than in the placebo group, and six months later the difference was 5·2 points. There was no significant difference as regards seizure recurrence over the two years in the two groups.

The data are not easy to interpret. Only children less than 12 months old or with risk factors for the development of later epilepsy[2] were entered into the study. At the start of the study the average Bayley mental index in those assigned to placebo was 103·6, in those assigned to phenobarbitone 104·8, and in age matched controls without seizures 113·8. The effect of phenobarbitone in depressing cognitive performance was less in the children who performed better at the outset. The results were analysed on an intention to treat basis but of 94 children assigned to placebo 29 were taking anticonvulsant treatment at two years after entry to the trial. Of 83 children in the phenobarbitone group only 53 were still taking phenobarbitone after two years. Seventy seven had intelligence testing at that time but only 46 of them were estimated on the basis of blood tests to have complied properly with treatment. Intention to treat analysis answers the question 'What happens to children assigned to treatment with drug X?'. It cannot answer the question 'What are the effects on children of taking drug X?'. Both questions are of interest. As regards the effect of phenobarbitone treatment (or rather, intention to treat) on seizure recurrence, the conclusion of this study is similar to that of the meta-analysis performed by Newton.[3] That analysis showed that sodium valproate was, if anything, less effective than phenobarbitone.

A similar study was reported from Cardiff by Aldridge Smith and Wallace in 1982,[4] and it seems extraordinary that that study is not mentioned in the American paper. In the Welsh study the children tested at two years had taken either the prescribed drug (phenobarbitone or sodium valproate) or no treatment throughout the study period. For children who had no recurrence of febrile convulsion the difference in mean Griffiths's development quotient between those untreated and those on phenobarbitone was 2·8 at the start of the study and 7·4 at the end, a difference assessed as statistically insignificant and due to an apparently greater rise in quotient in the children who took no drug. There was a small but (statistically) significant fall in developmental quotient after two years in the children who had further convulsions and a small rise in those who didn't. The authors therefore related poor intellectual progress to recurrence of convulsions rather than to drug treatment.

What conclusions can be drawn? Phenobarbitone treatment is commonly associated with behavioural side effects and its efficacy in preventing convulsions is at least questionable especially if results are analysed on the basis of intention to treat. There may be a small fall off in cognitive performance related to phenobarbitone treatment, although the practical as opposed to statistical significance is uncertain. It seems difficult to justify phenobarbitone prophylaxis for febrile convulsions unless the recurrence risk is very high and compliance is assured.

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ORIGINAL ARTICLES

Magnetic resonance imaging in neurological disorders

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Abstract

To investigate the role of magnetic resonance imaging (MRI) in neurological disorders, 115 children were studied in two groups. Group A (78 patients) was studied by paired computed tomography and MRI cranial scans. Group B (37 patients) was studied by paired computed tomography assisted myelography (CTM) and MRI spinal scans. In group A, the scans were generally equivalent for supratentorial tumours and for investigating fits, hydrocephalus, benign intracranial hypertension, and cerebral atrophies, but MRI scanning was superior for posterior fossa tumours and cysts. In group B, MRI scans were superior for intramedullary spinal tumours, spinal dysraphic problems with tethering or syrinx, and were complementary to CTM in diastematomyelia.

The advent of magnetic resonance imaging (MRI) has provided a further powerful tool for the investigation of diseases of the central nervous system. Current limited availability of scanning time and of health service resources, however, makes the prudent selection of patients for its use imperative.

Consequently, this study was devised to compare the usefulness of MRI cranial and spinal scans with cranial computed tomography and computed tomography assisted myelography (CTM). The study aims were to look at the role of MRI in childhood neurological disorders, to compare the accuracy of diagnosis with computed tomograms, and to identify the pathological entities where specific scanning modalities are preferable, and others where the modalities are equivalent or complementary. Thus the study hoped to identify the most appropriate initial investigation in certain clinical situations.

Subjects and methods

One hundred and fifteen children (60 girls and 55 boys) aged 2 days–17 years (mean 9·2 years) were studied. In group A, 78 children were studied with paired computed tomograms and MRI cranial scans. The scans were performed on the same day in most children, and all within two weeks of each other. In group B, 37 children were studied with paired CTM and MRI spinal scans. The imaging units used were the Picker 1200SX for computed tomography and a Picker 0·15 Tesla Resistive System for MRI scanning.

The scans in both groups were reported by the same neuroradiologist who was given the clinical details. The radiological diagnosis was then compared with the final clinical diagnosis. The scans were then graded for diagnostic value according to the following classification: grade 1—both scans were negative (normal); grade 2—both scans were positive and equivalent; grade 3—the MRI scan was superior to the computed tomogram; grade 4—the computed tomogram was superior to the MRI scan.

Informed parental consent was obtained before both computed tomography and MRI scanning.

Results

The results from comparing the radiological

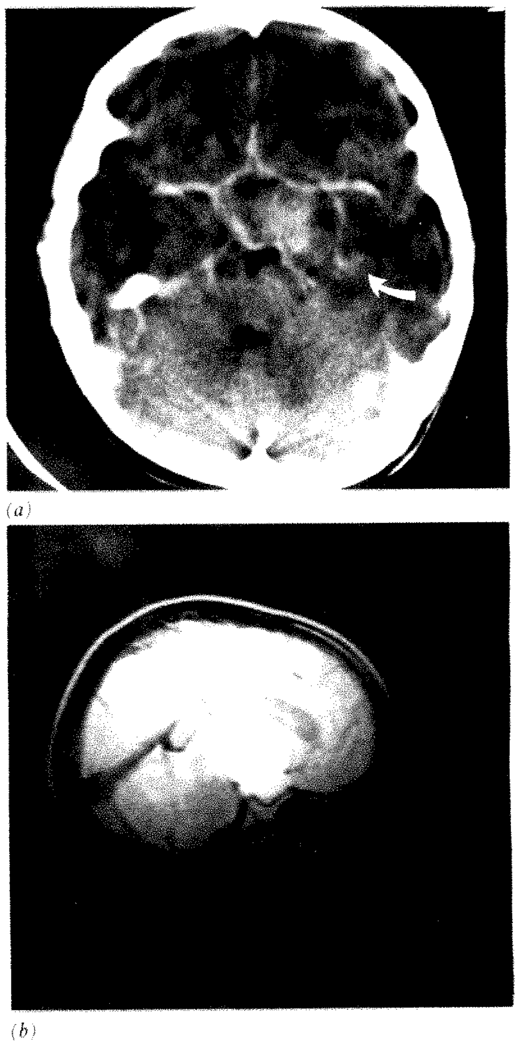


Figure 1 An 8 year old girl. (a) Computed tomogram showing tumour extension into the left geniculate region (curved arrow) of histologically proved optic chiasm glioma. (b) T2 weighted (TR=2000 msec, TE=80 msec) sagittal MRI scan demonstrating a large suprasellar high signal mass. As axial images were not obtained the posterior extension was not appreciated.

Table 1 Results of group A: computed tomography and MRI cranial scans

Pathology	*Both scans negative (grade 1)*	*Both scans positive (grade 2)*	*MRI superior (grade 3)*	*Computed tomography superior (grade 4)*	*Total*
(1) Tumours:					
(a) Supratentorial	—	16	4	1	21
(b) Infratentorial	1	5	8	—	14
(2) Cysts	—	2	3	—	5
(3) Hydrocephalus or benign intracranial hypertension	1	8	—	—	9
(4) Atrophic states	—	3	—	—	3
(5) Degenerative states	—	3	2	—	5
(6) Fits	8	3	—	—	11
(7) Miscellaneous neurological disorders	7	1	2	—	10
Total	17	41	19	1	78

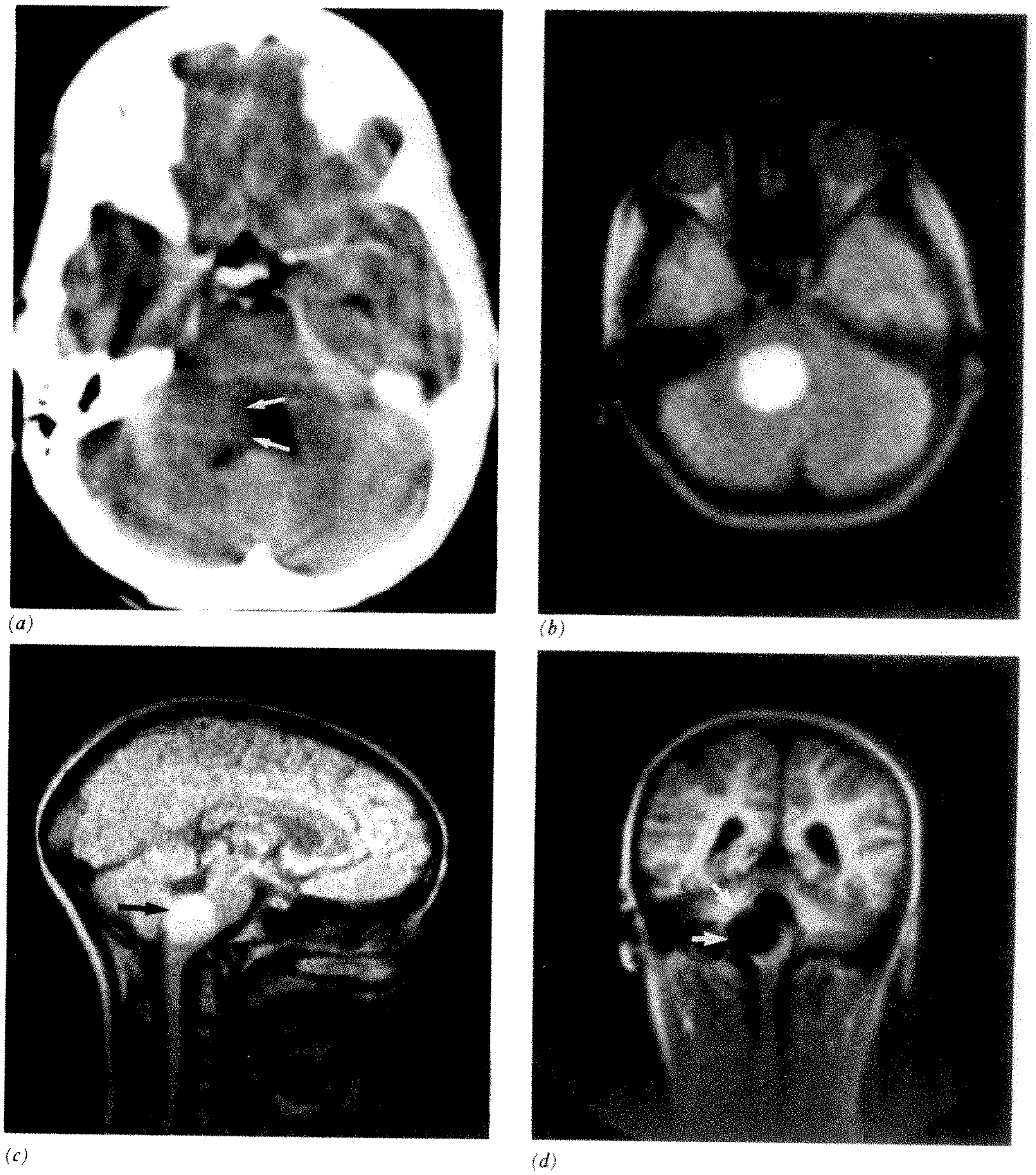

(*a*) (*b*) (*c*) (*d*)

Figure 2 A 12 year old girl. (a) Axial computed tomogram through the posterior fossa. An intrinsic lesion is inferred by the presence of tissue bulging into the right side of the fourth ventricle (arrows); however, tumour defintion is poor. (b) Axial and (c) sagittal T2 weighted (TR=2000 msec, TE=80 msec). (d) Coronal T1 weighted inversion recovery (TR=1660 msec, T1=400 msec) section clearly defines the lesion (arrows) and localises it within the brainstem and involves the right middle cerebellar peduncle (histology: brainstem glioma).

diagnosis and the final clinical diagnosis made on discharge for the two groups are shown in tables 1 and 2.

GROUP A (TABLE 1)

(1a) Tumours—supratentorial

There were 21 children with suspected supratentorial tumours. The scans in 16 (76%) cases were judged to be equivalent, whereas in four (19%) patients the MRI was superior in defining the anatomy and extent of the tumour. These four tumours included single cases of pilocytic astrocytoma, choroid plexus carcinoma, optic chiasm glioma, and mid brain glioma. The single case where the computed tomogram was adjudged to be superior had an optic chiasm pilocytic astrocytoma. The computed tomo-

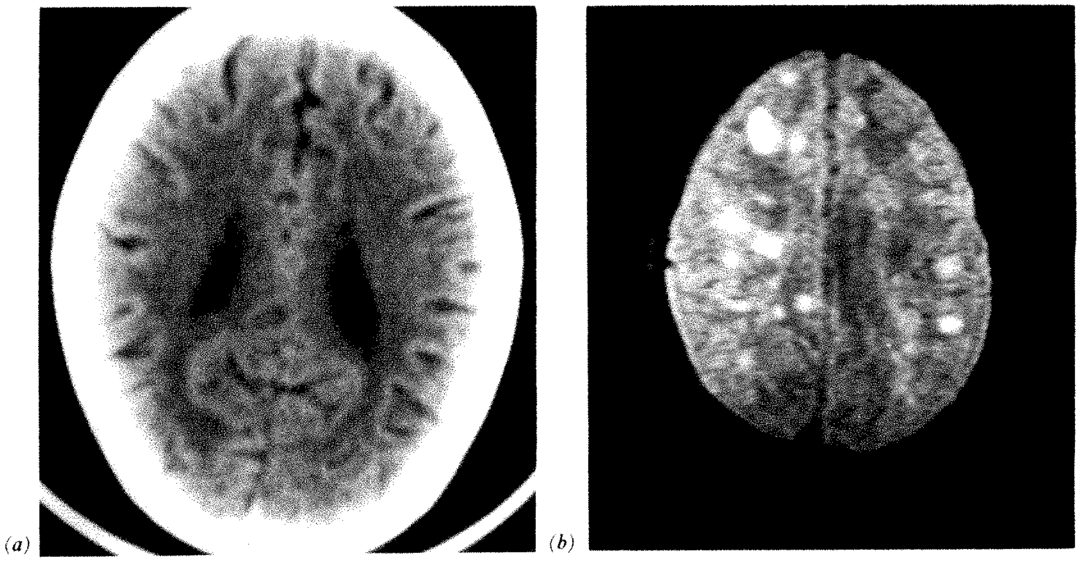


Figure 3 *A 7 year old boy. (a) Axial computed tomography section. Appreciable atrophy is present but no definite parenchymal lesion is seen. (b) Axial T2 weighted (TR=2000 msec, TE=80 msec) section shows multiple foci of high signal in the subcortical white matter of both cerebral hemispheres.*

Table 2 *Results of group B: paired CTM and MRI spinal scans*

Pathology	*Both scans negative (grade 1)*	*Both scans positive (grade 2)*	*MRI superior (grade 3)*	*CTM superior (grade 4)*	*Total*
(1) Spina bifida aperta/cystica	—	6	10	—	16
(2) Diastematomyelia	—	3	—	—	3
(3) Tight filum terminale syndrome (±syrinx)	—	1	3	1	5
(4) Spinal tumours (±syrinx)	—	2	3	1	6
(5) Miscellaneous spinal disorders	3	1	3	—	7
Total	3	13	19	2	37

gram showed posterior extension of the tumour along the optic tract. This extension was not well visualised on MRI, which had given the erroneous diagnosis of a hypothalamic glioma (fig 1). The appropriate use of axial magnetic resonance images, however, would probably have demonstrated clearly the full extent of the lesion along the specific pathways.

(1b) Tumours—infratentorial

The 14 children with suspected infratentorial tumours included a boy with symptoms of headache, ataxia, and nystagmus in whom both scans were negative and his symptoms subsequently resolved. In the remaining 13 children the studies were judged to be equivalent in five (39%) (three medulloblastomas, one brain stem

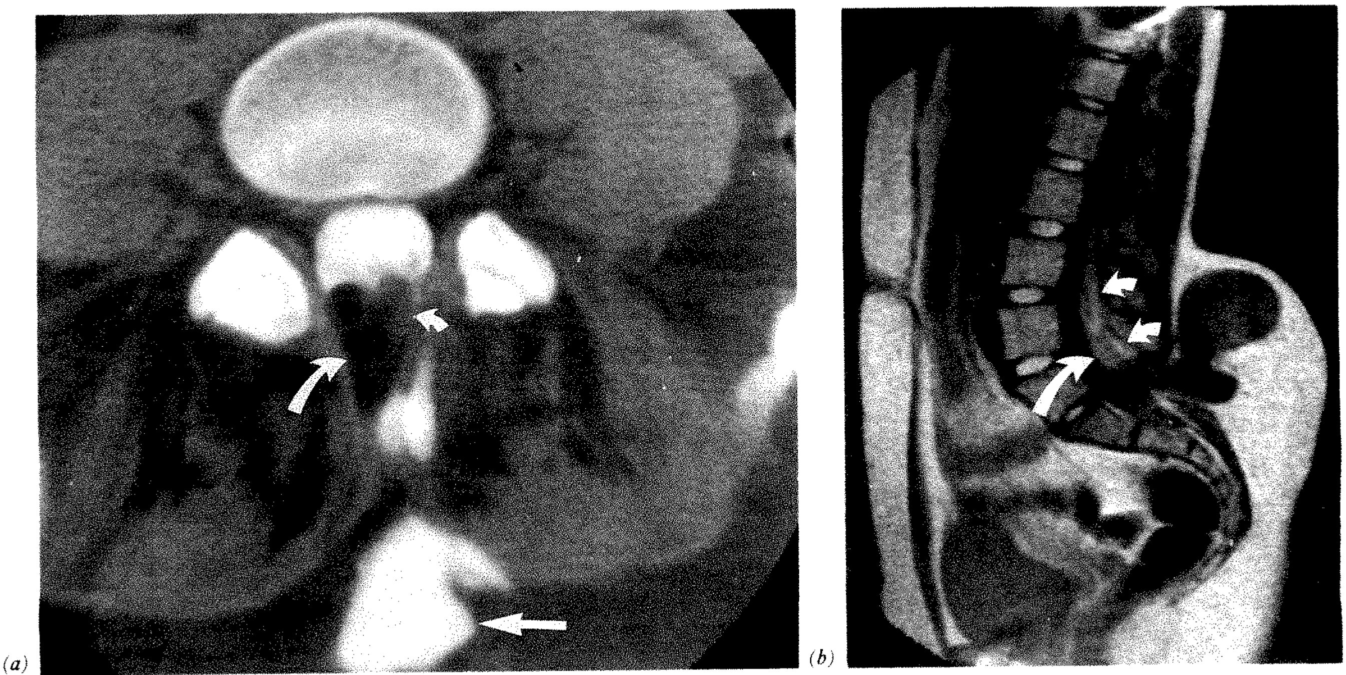


Figure 4 *A 13 year old girl. (a) Immediate postmyelographic axial computed tomogram through L5. Neural (short curved arrow) and lipomatous (long curved arrow) tissue is seen to pass posteriorly into a meningocele (straight arrow). Nerve roots can be seen arising from the anterior surface of the low cord. (b) T1 weighted (TR=500 msec, TE=40 msec) sagittal scan. The relationship of the higher signal lipomatous tissue (short curved arrows) can be clearly seen, lying on the dorsal surface of the cord (long curved arrow), both passing posteriorly into the bilobed meningocele.*

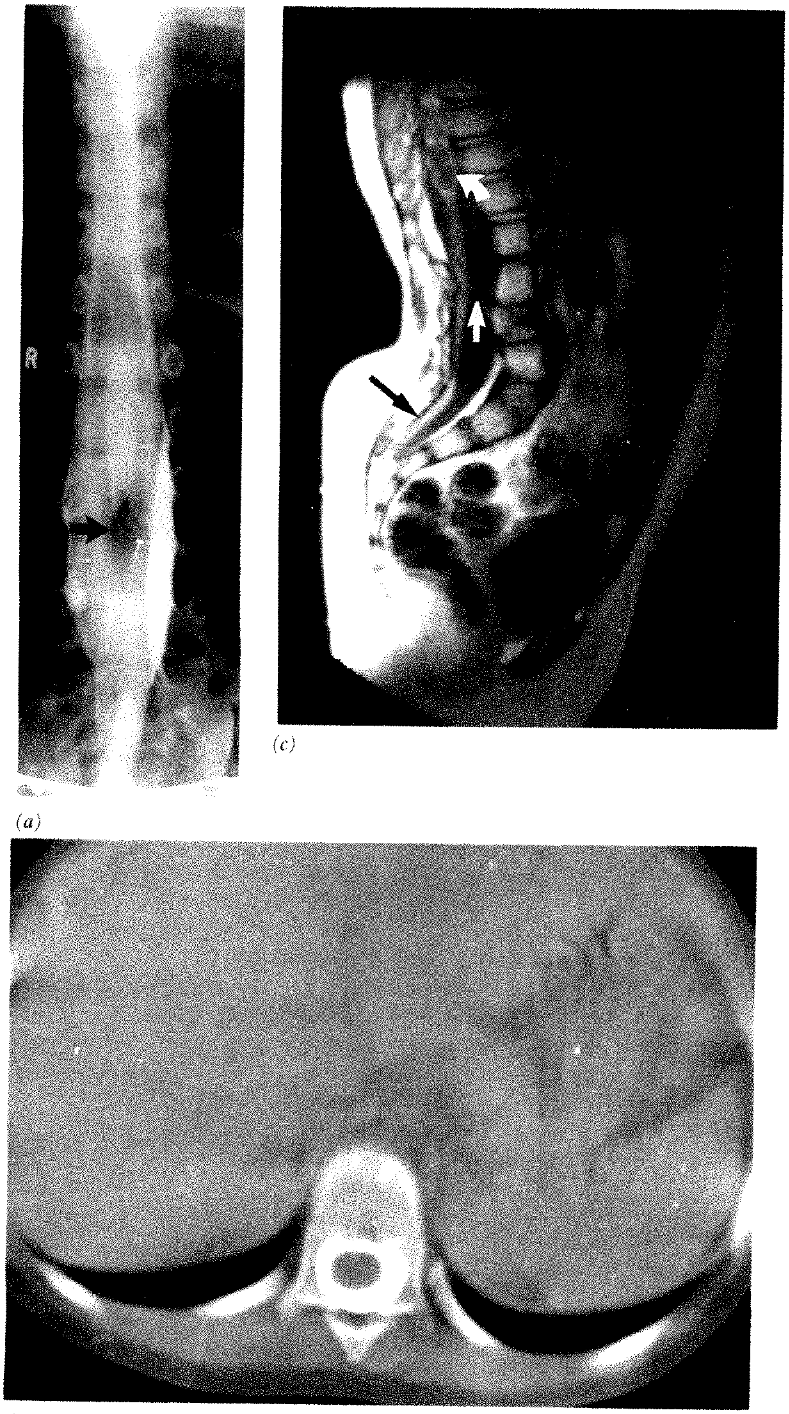


Figure 5 A 3 year old girl. (a) Anterior-posterior view from myelogram showing the classical appearances of a double arachnoid-dural sac diastematomyelia with an interposed bone spur (arrow). The cord above the split appears a little bulky. (b) Postmyelographic computed tomogram through the cord at the T12 level shows no obvious abnormality. Delayed scanning was not performed. (c) T1 weighted (TR=500 msec, TE=40 msec) sagittal scan demonstrates a septated syringohydromyelic cavity in the cord above the cleft (curved arrow). The fibro-osseous spur (straight white arrow) is seen. An unsuspected filar lipoma (straight black arrow) is noted.

glioma, one juvenile astrocytoma) and the MRI was superior in eight (62%) (three cerebellar astrocytomas (fig 2), two medullary astrocytomas, and single cases of medulloblastoma, brain stem glioma, and a tectal plate glioma). In all cases where a tumour was present, however, an abnormality was picked up by both imaging modalities.

(2) Cysts
Five patients had cystic lesions, of which four were arachnoid cysts. In three the MRI scan was judged to be superior, defining the complicated anatomical connections particularly when the posterior fossa was involved.

(3) Hydrocephalus or benign intracranial hypertension
Nine children had suspected hydrocephalus or benign intracranaial hypertension. In the one patient with benign intracranial hypertension both scans were normal. In the remaining eight cases with hydrocephalus abnormalities were detected equally well by both techniques.

(4) Atrophic states
Three children had atrophic states clearly demonstrated by either scan.

(5) Degenerative states
Five children were investigated for suspected degenerative disorders, of whom in one case each of Krabbe's leucodystrophy, Wilson's disease, and optic neuritis the scans were equivalent. However, in two children the MRI was superior demonstrating pathology not seen on the computed tomogram. One had Leigh's disease with a left medullary lesion demonstrated, and the other had florid changes of demyelination (fig 3) not seen on the computed tomogram.

(6) Fits
Eleven children were investigated for troublesome focal fits whose electroencephalograms had suggested an underlying structural abnormality. In eight both scans were normal. In the remaining three both scans identified the abnormalities including one with tuberous sclerosis, one with cerebral atrophy, and one with cogenital hamartoma.

(7) Miscellaneous neurological disorders
Ten children had a variety of suspected or known neurological disorders. In seven both scans were negative. One child had a lentiform nucleus infarct clearly seen on both scans. The MRI was superior in two, identifying a cavum septum pellucidum in one, and haematomas secondary to vasculitis in the other.

For the whole of group A (table 1) 58 out of 78 (74%) scans were equivalent (either positive or normal). In one child the computed tomogram was superior, and in 19 (24%) the MRI was superior, particularly with posterior fossa tumours and cysts and certain degenerative disorders.

GROUP B (TABLE 2)
(1) Spina bifida aperta/cystica
Sixteen patients were investigated after the development of new neurological signs suggesting cord tethering or cavitation. In six the scans were judged to be equal, but in 10 the MRI was superior particularly in subjects with lipomyelomeningoceles in the lumbosacral region (fig 4).

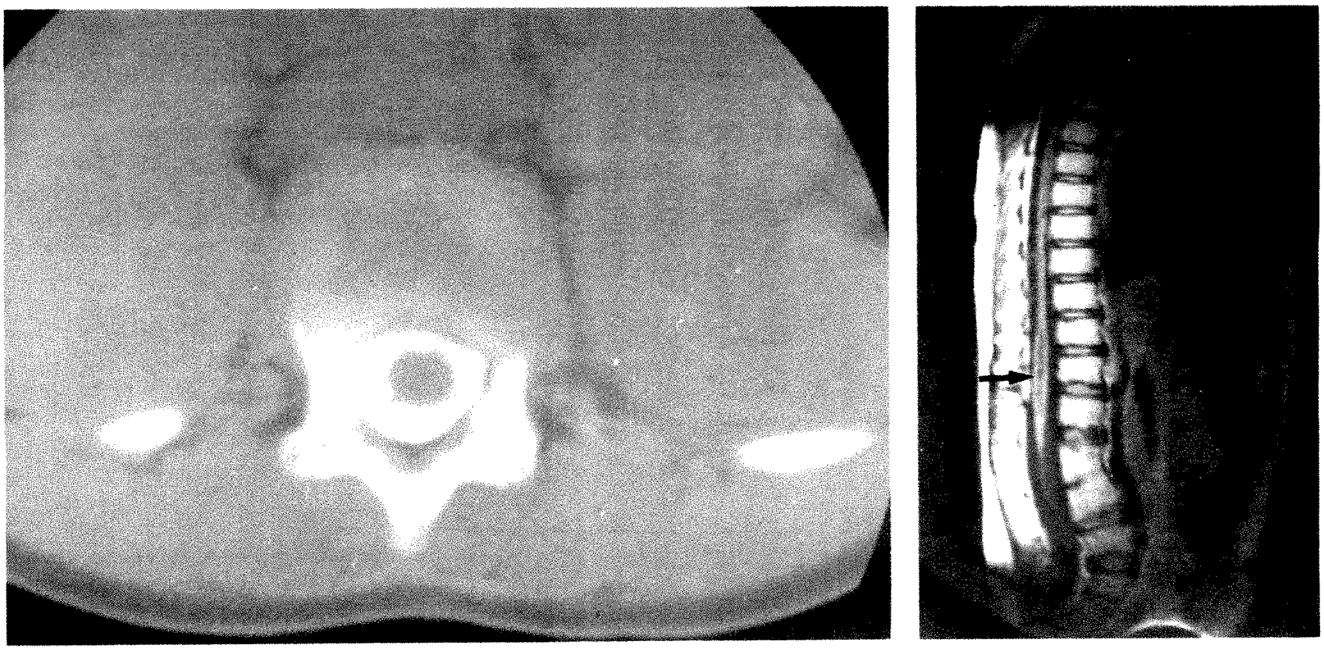

(a) (b)

Figure 6 A 12 year old boy. (a) Postmyelographic computed tomogram shows an apparently normal distal thoracic cord. Delayed scanning was not performed. (b) T1 weighted (TR=500 msec, TE=40 msec) scan shows a linear central syringohydromyelic cavity (arrow) in a low lying cord. The thickened tethering filum terminale was better demonstrated by computed tomography.

(2) Diastematomyelia
Three patients had diastematomyelias which were equally well demonstrated by both imaging techniques. While CTM more clearly defined the finer neural detail and fibro-osseous septum, if present, between the two hemicords, MRI provided additional information as to the presence of associated cord cavitation (seen in two of the cases) (fig 5).

(3) Tight filum terminale syndrome
Five children had a tight filum terminale syndrome. In one the scans were of equivalent value. In three the MRI scan was superior, demonstrating an associated syrinx in two (fig 6), and in the other with kyphoscoliosis showing cord thinning. A single child with arthrogryposis and scoliosis had cord tethering which was more clearly defined by CTM.

(4) Spinal tumours
Six children had spinal tumours; in three the MRI was the superior examination (fig 7) whereas in two the studies were equal. A single

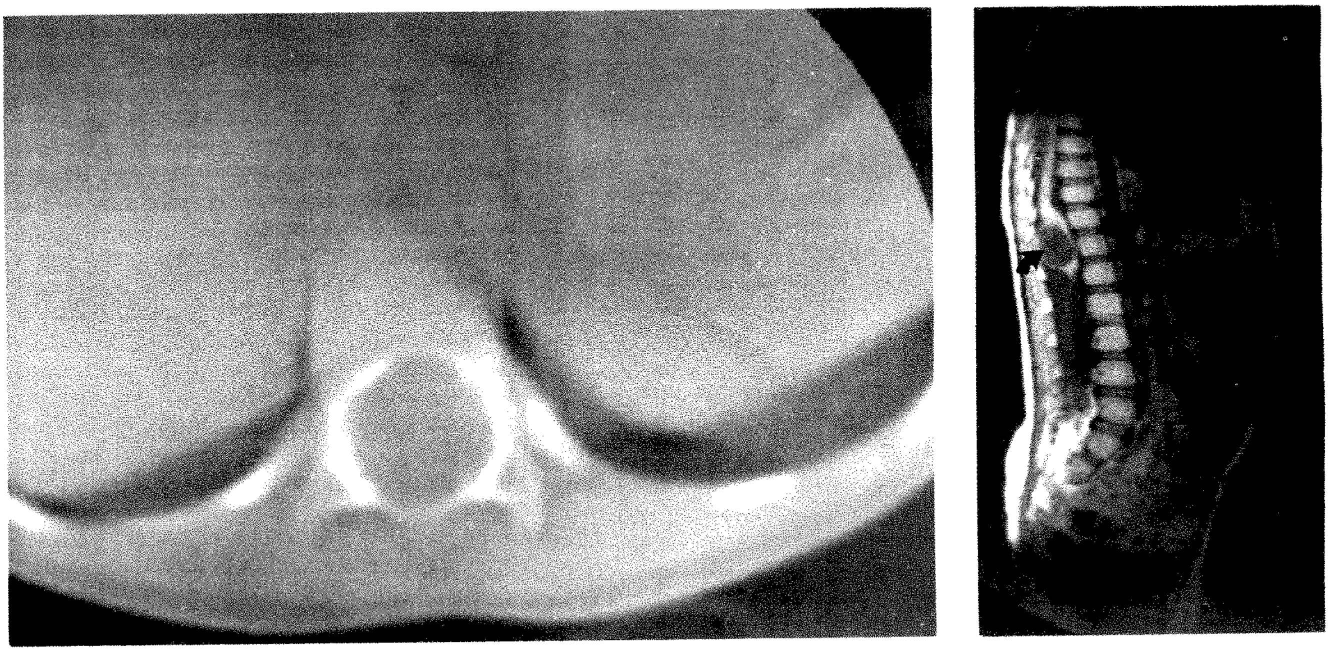
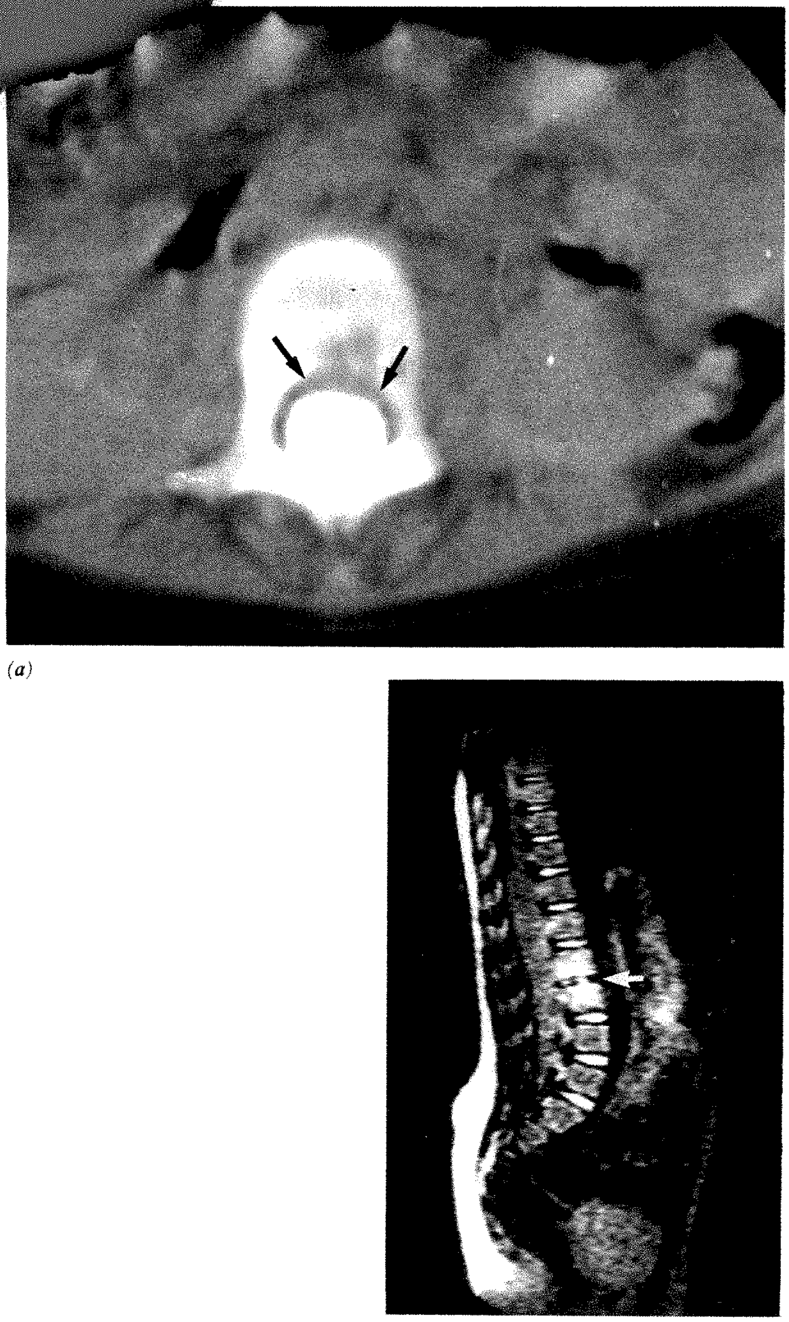

(a) (b)

Figure 7 A 2 year old girl. (a) Postmyelographic computed tomogram. There is diffuse expansion of the cord at T12, but lesion definition and tissue characterisation is poor. (b) T1 weighted (TR=500 msec, TE=40 msec) sagittal section demonstrates a well circumscribed cystic structure felt to represent an intramedullary dermoid, confirmed at surgery.


(a)

(b)

Figure 8 A 3 year old girl. (a) Postmyelogram computed tomogram shows a small amount of extradural soft tissue (arrows) indenting the anterior theca. Subtle end plate changes can be seen in the posterior aspect of the vertebral body. (b) Sagittal STIR ($TR=1100$ msec, $T1=100$ sec). Florid high signal is seen in the bodies of L2 and L3 adjacent to the abnormal interposed disc which shows signal reduction and loss of height, features characteristic of discitis.

girl had intrathecal droplet metastases seen on CTM that could not be demonstrated with certainty by MRI.

(5) Miscellaneous spinal disorders
Three children with bladder dysfunction or long tract signs, or both, had normal scans. The scans were equally informative in one child with mesodermal dysplasia. The MRI was superior in three children, including one with cervical cord trauma from a knife stab wound, one after previous scoliosis surgery with an associated lipoma, and a girl with discitis (fig 8).

Thus in group B (table 2) the imaging techniques were equivalent in 16 out of 37 (43%) (either positive or negative), the MRI was superior in 19 (51%) and CTM was better in two (5%).

Discussion

In certain fortunate centres the availability of a full range of imaging methods enables possible neurological problems to be investigated in various alternative ways. In many district and referral hospitals, however, MRI scanning, and even computed tomography, may not be freely available. Given the current concerns about scarce health resources it is important that children are investigated by the most appropriate method. We have attempted to suggest possible guidelines for the use of MRI scanning.

The performance of both scans has possible advantages in yielding greater certainty of diagnosis and providing complementary information. Greater expertise in the scanning techniques may also result. In addition even though an additional scan may not alter the diagnosis it may well aid the neurosurgeon in planning operative intervention such as the case shown in fig 9, where the computed tomogram showed a large enhancing mass based on the left thalamus, considered to be inoperable by the neurosurgeon. The magnetic resonance scan, however, showed a well circumscribed lesion adjacent to the skull base, which was felt to be accessible by a subtemporal approach. This was successfully done leaving the child with minor disability only.

The coronal plane most nearly approximates to the operative field in posterior fossa tumours and the siting and extent of the necessary craniotomy can best be assessed from such sections. Posterior and inferior extension of tumour into the vallecula, cisterna magna, and upper cervical canal; lateral extension into the cerebellar peduncles and cerebellopontine cisterns and superior extension through the tentorial hiatus can be readily assessed from the coronal perspective.

The indiscriminate use of both scanning methods would, however, be wasteful of often limited resources with an average cost in our unit for an enhanced computed tomogram of £155 and for an MRI cranial scan of £206. Average costs of CTM are £312, and for an MRI spinal study £206. Performing both scans can place an extra burden upon the patient and family, as well as necessitating longer hospitalisation and potentially straining the family's resources to cover the hospital stay.

Although the numbers were not large, this study showed that MRI and computed tomography cranial scans gave identical information when investigating the possibility of a structural lesion in a child with epilepsy. Previous reports have suggested the superiority of MRI scanning in this clinical situation.[1 2] Our advice would be to do computed tomography, and if the scan is negative consider requesting an MRI scan only if seizures are difficult to control despite optimal anticonvulsant treatment.

Similarly, in most children with hydrocephalus, benign intracranial hypertension, or cerebral atrophies either scanning method

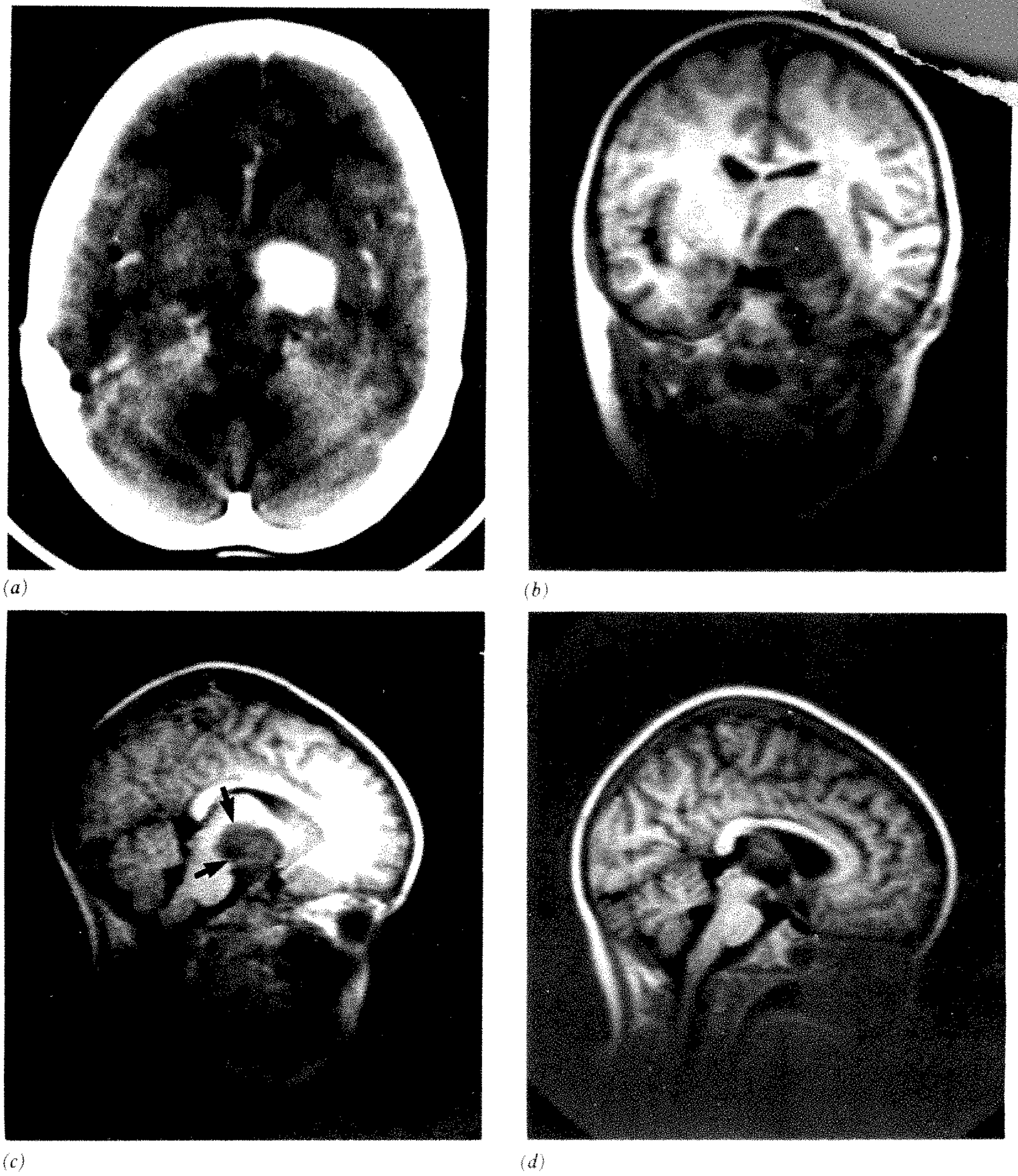


Figure 9 A 7 year old girl. (a) Enhanced axial computed tomogram demonstrating a rather poorly defined strongly enhancing lesion in the deep left temporal region, extending to the left cerebral peduncle. (b) Coronal and (c) sagittal T1 weighted (SE 500 msec, TE=40 msec) sections show a clearly defined low signal lesion (arrows). On the basis of the coronal scan the neurosurgeon felt that a subtemporal approach was feasible and a macroscopic resection obtained. (d) Six months postsurgical T1 weighted section. No tumour residuum demonstrated (pathology: juvenile pilocytic astrocytoma).

(according to the ease of availability) could be expected to yield the same information.

Posterior fossa tumours and cysts are usually best investigated by MRI.[3-5] Suspected supratentorial lesions can be investigated initially by either method, although it appears that in most cases the MRI scan will be at least as good as the computed tomogram.

In children with complicated spinal dysraphic abnormalities, particularly those with associated lipomas, the MRI scans tend to be more informative.[6] Similarly in children with intramedullary spinal tumours the MRI scans yield greater information. However, subtle metastatic deposits may be more clearly seen on CTM.

In the investigation of children with diastematomyelia the two methods tend to be complementary. However, MRI is consistently superior for the demonstration of unsuspected or occult cord cavitation.

It is especially in the sphere of dysraphic lesions and assessment of childhood kyphoscoliotic states that close liaison between the referring clinician and neuroradiologist is essential to optimise the diagnostic information from magnetic resonance scanning. The choice of correct imaging parameters may considerably enhance the accuracy of the examination. In particular the appropriate use of pulse sequences will reduce the risk of failing to identify subtle intraspinal lesions and enable more precise tissue characterisation.

In children with degenerative disorders such as multiple sclerosis,[7 8] and for studying myelination disorders and patterns in infancy, MRI scanning provides clearer and more accurate information.[9 10]

This study has been based upon the comparison between computed tomography and a low field (0·15 Tesla (T)) MRI system. It is accepted that imaging employing mid or high field systems considerably improves the diagnostic accuracy and resolution capabilities of this modality. The field homogeneity at 0·15T is suboptimal and the inability to obtain cardiorespiratory gating produced relatively poor quality imaging in the spine. The wider use of higher field systems will lead to improved spinal imaging especially when coupled with fast sequences and improved surface coils. An advantage of a low field system has been the ability to perform general anaesthetics with minimal modification of the equipment. Most patients scanned in our study, however, were given oral sedation only. Where possible selection of the shorter T1 weighted spin echo sequences enabled a reduction in the overall scan time.

Since this study the introduction of gadolinium diethylene triamine pentacetic acid (DTPA) has considerably improved the imaging capabilities of MRI with the ability to define intrinsic and extrinsic central nervous system pathology with greater sensitivity. It is foreseen that this will lead to the more frequent use of MRI scanning in the neuraxis.

In conclusion, where MRI imaging is not freely available, we would recommend that it is best reserved for children with a suspected posterior fossa tumour or cyst, for complicated spinal abnormalities, and for certain suspected degenerative disorders. Furthermore, MRI enables the use of potential frequent or serial scanning without the attendant risks of a heavy radiation burden to this young group of patients.

We thank Mr J Punt, Mr T Hope, and Mr J Firth for permission to study children who were under their care.

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Slow release carbamazepine in treatment of p controlled seizures

S W Ryan, I Forsythe, R Hartley, M Haworth, C J Bowmer

Abstract

Thirty three children with poorly controlled epilepsy, and six new patients, were treated with slow release carbamazepine. Twelve of the former had a reduction in the number of seizures of more than half, and 10 had fewer side effects. Three of the new patients stopped having seizures. Variations in plasma concentrations between doses was significantly less when patients took the slow release preparation (22%) compared with the standard preparation (41%). Slow release carbamazepine may improve the conditions of children whose seizures are poorly controlled.

Carbamazepine is the first choice of drug for the treatment of children with tonic-clonic and complex partial seizures.[1–4] Giving treatment twice daily has been recommended to simplify administration, aid compliance, and avoid the necessity of teachers having to dispense the drug during school hours.[3 5 6] We have shown, however, that because of the short half life of carbamazepine, there is a significant difference in plasma carbamazepine concentrations between the maximum (peak) and the minimum (trough) in patients receiving doses twice daily.[7] Experience has shown that seizures are more likely to occur during troughs, particularly in the morning on awakening, whereas side effects are often associated with peaks.[8 9]

Until the recent introduction of slow release preparations of carbamazepine the only way of diminishing the effects of troughs and peaks was to increase the number of doses. This presented difficulties in dispensing the drug at school, and lead to poorer patient compliance.[3 5 6] Despite minimising plasma fluctuations during the day by this approach, the problem of dividing doses equally during the night remains. As this is not practicable because of children's sleeping patterns, the early morning troughs persist. Furthermore, attempts to vary the dose during the day to take account of the irregular dosing intervals, may lead to confusion among patients and paediatricians.

A slow release preparation should, however, provide a smoother plasma concentration-time profile, with smaller peaks and shallower troughs, thus permitting twice daily dosage. In view of the increased cost of such a preparation it is important to assess its clinical effectiveness and its pharmacokinetic profile. If these are satisfactory, the preparation would be a useful addition to the anticonvulsant formulary.

Consequently, when slow release carbamazepine became available (Tegretol CR Divitabs, Ciba Geigy) we assessed its effects.

Patients and methods

The study was approved by the hospital ethics committee. Thirty three children with poorly controlled epilepsy who were suffering from generalised tonic-clonic (n=25) or complex partial seizures (n=8) were identified during a one year period. In addition six new patients with tonic-clonic seizures who had not yet received treatment were also studied. They all started drug treatment if three seizures, each of more than five minutes duration, had occurred during a period of six months. When such children were identified the study was explained to the parents and child and consent obtained. There were no refusals.

All 33 children with poorly controlled seizures had received standard carbamazepine twice daily, and later some had been given carbamazepine and acetazolamide, sodium valproate, mysoline, bromide, or phenytoin (table 1). In patients who had previously been treated with carbamazepine, the dosage of slow release carbamazepine/kg body weight that was given was similar to the previous dose, except for two patients, in whom the previous dose was felt to be inadequate and so a higher dose of slow release carbamazepine was prescribed.

Those receiving acetazolamide were allowed to continue, as we regarded it as unethical to discontinue it at this stage. Patients on other drugs were changed over a period of two to three weeks to slow release carbamazepine.

After the patients had been treated for 30 to 100 days they were admitted overnight so that blood samples could be taken to provide measurements of the pharmacokinetic profile of the slow release preparation. The skin was anaesthetised with 2·5% lignocaine and prilocaine cream (Emla, Astra), and an indwelling venous cannula was inserted. At 2000 the first sample was taken to assess compliance. The following day samples were taken at hourly intervals (0800–1200) and then every two hours until 2000. On each occasion a 3 ml sample was obtained after adequate flushing of the cannula to avoid dilution with heparin; samples were then stored at 4°C for 36 hours before separation.

Plasma concentrations of carbamazepine were measured by an established method with high performance liquid chromatography.[10] Mean peak and trough plasma concentrations of carbamazepine were calculated and the interdose fluctuations were calculated as the percentage

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Table 1 Details of patients studied

Case No	*Sex*	*Age (years)*	*Weight (kg)*	*Previous drugs, dose, and timing*	*Initial dose of slow release carbamazepine (twice a day, mg)*	*Other features*
Children with tonic-clonic seizures:						
1	Male	4	20	Carbamazepine 200 mg twice a day	200	Mental retardation
2	Female	4	17	Carbamazepine 200 mg 3 times a day	300	Atonic
3	Female	5	29·5	Mysoline 125 mg 3 times a day	300	None
4	Female	5	25	Carbamazepine 150, 100, and 200 mg	200	None
5	Male	6	32	Carbamazepine 200 mg 3 times a day	300	None
6	Female	7	40·5	Phenytoin 100 mg twice a day	400	Atonic
7	Male	7	24	Bromide	200	Focal right sided seizures
8	Female	8	23	Carbamazepine 150 mg 3 times a day	200	Focal left sided seizures
9	Female	9	38	Sodium valproate 200 mg 3 times a day	300	None
10	Male	9	34	Carbamazepine 300 mg 3 times a day	400	None
11	Female	10	32	Carbamazepine 200 mg 3 times a day	300	Atonic
12	Female	10	29	Carbamazepine 200 mg 3 times a day	200	Focal left sided seizures
13	Female	10	40	Mysoline 250 mg 3 times a day	400	None
14	Male	10	39	Carbamazepine 200, 200, and 400 mg	500	Left hemiplegia
15	Male	10	32	Carbamazepine 200 mg twice a day	200	None
16	Male	10	31	Carbamazepine 100 mg 3 times a day	300	Tuberous sclerosis
17	Male	11	23	Carbamazepine 150 mg 3 times a day	200	Spastic quadriplegia
18	Male	11	46·5	Carbamazepine 800, 600, and 600 mg, and acetazolamide	1000	Operation to frontal lobe
19	Male	12	57	Carbamazepine 200, 200, and 400 mg	400	None
20	Male	12	45	Carbamazepine 200, 200, and 400 mg	400	Hemiplegia
21	Male	14	52	Carbamazepine 400, 200, and 600 mg	600	None
22	Female	14	62	Carbamazepine 200 mg twice a day	100	None
23	Male	15	60	Carbamazepine 400 mg 3 times a day	600	None
24	Female	16	48	Carbamazepine 400 mg twice a day	500	None
25	Male	16	Not known	Carbamazepine 500 mg twice a day	500	Focal right sided seizures
Children with complex partial seizures:						
26	Male	5	22	Carbamazepine 200 and 300 mg	200	Hemiplegia
27	Male	8	23	Carbamazepine 200 mg twice a day	200	None
28	Female	9	35·5	Carbamazepine 400 and 800 mg	600	None
29	Male	11	46·5	Carbamazepine 200, 200, and 400 mg	400	None
30	Female	12	48	Carbamazepine 300 mg 3 times a day, and acetazolamide	500	None
31	Female	13	52·5	Sodium valproate 700 mg twice a day	600	None
32	Female	14	47	Carbamazepine 200 mg twice a day	200	None
33	Female	14	39	Carbamazepine 200 mg 3 times a day	600	None

decrease from peak to trough concentration (100(peak−trough)/peak).

Comparison of the mean peak (1200) and trough (2000) concentrations were made with Student's *t* test for paired samples. In addition the mean peak and trough concentrations from a subgroup of 16 patients receiving a daily dose of 14 to 20 mg/day slow release carbamazepine were compared with the corresponding concentrations in children taking similar doses of standard carbamazepine. The interdose fluctuation in concentrations obtained from the subgroup of patients receiving slow release carbamazepine was also compared with that in children taking the standard preparation. In all cases comparisons of mean carbamazepine plasma concentrations and the interdose fluctuations between patients receiving slow release carbamazepine or the standard preparation were made with Student's *t* test for unpaired samples.

Once the plasma carbamazepine concentrations had been calculated, the patients' responses were analysed. If seizures recurred, the dose was increased (provided that plasma carbamazepine concentration indicated that this was reasonable), or they were changed back to their original preparation, or they were given a different preparation (for example, oxcarbazepine). Results of the adjustments and changes in treatment are shown in tables 2 and 3.

All parents and patients were asked to keep an accurate record of seizures, and in the group of poorly controlled children, diaries were well kept. Each time a patient was seen at the clinic the number, type, duration, and severity of seizures was recorded by the doctor.

When the study was completed the duration of treatment and the number of seizures were noted. An equal retrospective time period from the onset of the medication change was also noted, and the number of seizures occurring during that period was recorded for comparison. In this way we hoped to assess any therapeutic benefit of the new preparation. The length of periods of observation are shown in tables 2 and 3.

In addition, parents were asked to note any change that occurred in their child after the drug was changed to identify benefits as well as adverse side effects.

Results

SEIZURES

The results for individual patients are shown in table 2. Of 25 patients with poorly controlled tonic-clonic seizures, five (20%) had no seizures while taking slow release carbamazepine (although two had had no seizures in either the treatment or the control period); in six (24%) the number of seizures was reduced by more than half; nine (36%) showed no change in their seizure pattern; in one (4%) the frequency of seizures increased by more than half; and in four (16%) the frequency more than doubled. Thirteen patients (52%) remained on unadjusted doses of slow release carbamazepine, four (16%) had their doses increased, two (8%) were given acetazolamide in addition, two (8%) reverted to their original treatment, and four (16%) received new forms of treatment including two (8%) who were prescribed oxcarbazepine. All four patients who had their doses of slow release carbamazepine increased had a decrease in the frequency of seizures.

Of the eight patients with complex partial seizures, one had complete control of seizures (but was also free of seizures in the control period); in three (37%) the number of seizures was reduced by between a half and three quarters; four (50%) were unchanged, and one was worse. Five patients remained on slow release carbamazepine and two of these had the dose increased without further improvement in seizure control.

Of the six new patients who were given slow release carbamazepine, three were free of seizures on follow up after 62 to 182 days, having previously had between two and four seizures during the control period (table 3). One patient experienced pronounced deterioration in seizure control (from one seizure in 136 days during the control period to 195 seizures during the period of treatment). This patient's condition however, constantly changed after a cerebral infarct, and other treatments were equally ineffective.

SIDE EFFECTS

Of the 33 patients, 10 (30%) experienced some side effects. In seven (21%) transient diplopia, vertigo, or bad temper were noted. Only three patients (9%) had persistent adverse side effects, and in two of these treatment was discontinued. One patient experienced screaming and photophobia, the other slurred speech and ataxia. The remaining patient complained of tiredness, which persisted, but elected to continue treatment as the seizures were controlled. In this patient trough and peak plasma concen-

Table 2 Number of seizures that occurred when patients changed to slow release carbamazepine compared with the number that occurred when taking previous treatment over a comparable period, and further changes in treatment made during the study

Case No	Study period (days)	No of seizures		Further changes in treatment made during the study
		While taking previous treatment	While taking slow release carbamazepine	
Children with tonic-clonic seizures:				
1	14	18	100	Standard carbamazepine restarted
2	168	30	30	Oxcarbazepine started
3	188	8	24	Dose of slow release carbamazepine increased to 500 mg twice a day on day 75
4	135	6	23	Sodium valproate started
5	238	4	1	None
6	211	12	4	None
7	71	6	90	Phenytoin started
8	24	0	0	None
9	168	7	3	None
10	254	1	0	None
11	167	7	6	Acetazolamide added to regimen
12	147	93	60	Dose of slow release carbamazepine increased to 500 mg twice a day on day 93
13	210	36	26	Acetazolamide added to regimen
14	19	2/Day	3/Day	Restarted standard carbamazepine because of side effects
15	62	0	0	None
16	200	100	130	None
17	233	1	1	None
18	52	9	5	None
19	166	10/Day	3/Day	Dose of slow release carbamazepine increased to 600 mg twice a day on day 81
20	187	5/Day	5/Day	Dose of slow release carbamazepine increased to 600 mg twice a day on day 84
21	206	4	1	None
22	63	1	0	None
23	139	3	1	None
24	217	49	0	None
25	29	12/Day	8/Day	Oxcarbazepine started
Children with complex partial seizures:				
26	218	36	28	Dose of slow release carbamazepine increased to 300 mg twice a day on day 58
27	232	20	4	Dose of slow release carbamazepine increased to 300 mg twice a day on day 155
28	126	31	27	None
29	256	0	0	None
30	98	61	38	Oxcarbazepine started
31	191	100	43	Oxcarbazepine started
32	35	4	1	Mysoline started because of side effects
33	45	9	14	None

Table 3 Details of six patients with tonic-clonic seizures who received slow release carbamazepine as their first anticonvulsant treatment

Case No	Sex	Age (years)	Weight (kg)	Dose (twice a day)	Study period (days)	No of seizures		Changes made in treatment during period of study
						Before treatment	After starting treatment	
34	Male	13	55·5	600	182	2	0	None
35	Female	11	43	400	62	2	0	None
36	Male	9	20	200	7	Study period too short to assess frequency		Sodium valproate started
37	Female	7	28·5	300	85	4	0	None
38	Male	4	25	300	136	1	195	Phenytoin started
39	Male	15	58·4	400	7	Study period too short to assess frequency		Phenytoin started

trations of carbamazepine were 35·9 and 47·4 µmol/l, respectively. Beneficial side effects were observed in 10 patients, these included improved behaviour and school performance, less vertigo, and less sedation (six had changed from standard carbamazepine, and four from other drugs).

Of the six new patients who were treated with slow release carbamazepine, two developed rashes, and treatment was discontinued. The rash in one persisted on sodium valproate and was eventually diagnosed as acne with follicular eczema.

In all, 14 of the 33 patients (42%) who had previously received anticonvulsant treatment (reduced frequency of seizures in 12, reduced side effects in 10) and three new patients obtained some benefit from treatment with slow release carbamazepine.

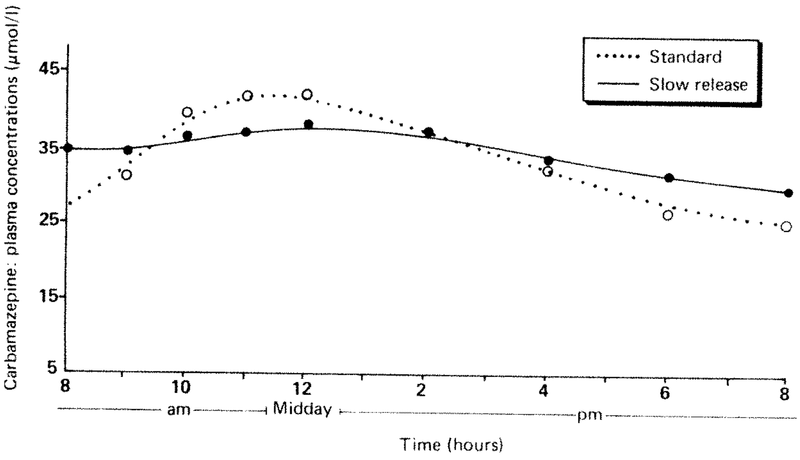
PLASMA CONCENTRATIONS OF CARBAMAZEPINE

Of the 39 children recruited into the study, 28 satisfied the criteria for inclusion of data on plasma concentrations for statistical analysis. Eleven patients were not included because two were receiving acetazolamide, four changed treatment before analysis, and in five patients samples were not available at a suitable time. Consequently, in 28 patients taking slow release carbamazepine (mean (SD) daily dose 19·3 (5·4) mg/kg) the mean (SD) peak plasma concentration at 1200 was 37·3 (7·5) µmol/l and mean (SD) trough concentrations were 33·3 (9·1) and 29·4 (7·6) µmol/l at 0800 and 2000, respectively. The differences between peak and trough concentrations of carbamazepine were significant ($p<0·001$). Similar peak and trough values for plasma carbamazepine were calculated for 16 children who received between 14 and 20 mg/kg/day of slow release carbamazepine (mean 17·7 (1·8) mg/kg/day). These values were compared with those obtained in 18 children receiving a standard formulation of carbamazepine in the same dose range (16·9 (1·7) mg/kg/day) (table 4). Comparisons of these mean plasma concentrations between treatment groups showed no significant difference between peaks ($p>0·05$), but troughs were significantly lower ($p<0·01$ and $p<0·05$ at 0800 and 2000, respectively) in the group of patients receiving standard carbamazepine. The interdose variation in carbamazepine plasma concentrations was 21·3% for the total population of 28 receiving slow release carbamazepine, 21·5% for the subgroup of 16 patients receiving 14 to 20 mg/kg/day of slow release carbamazepine, and 41% for the 18 patients receiving comparable doses of the standard carbamazepine preparation.

Table 4 Plasma concentrations of carbamazepine in children receiving comparable doses of standard compared with slow release preparations in the dose range 14–20 mg/kg/day

Time	*Mean (SD) carbamazepine concentration (µmol/l)*		*p Value*
	Slow release (n=16)	*Standard (n=18)*	
0800 (trough)	34·6 (7·9)	26·8 (4·3)	<0·01
1200 (peak)	38·1 (7·0)	42·3 (6·8)	>0·05
2000 (trough)	29·9 (7·6)	25·2 (4·9)	<0·05

The carbamazepine peak:trough plasma level ratio was 1·27 for slow release carbamazepine in both the total group of patients and the subgroup of 16 patients who were receiving doses ranging from 14 to 20 mg/kg/day. In 18 patients treated with the standard carbamazepine preparation in comparable doses (14 to 20 mg/kg/day), however, the ratio was 1·68.



Plasma concentrations of carbamazepine in children treated with comparable doses (14 to 20 mg/kg/day) of standard and slow release carbamazepine.

Discussion

For the purpose of this discussion slow release carbamazepine-CG refers to Ciba Geigy carbamazepine (Tegretol CR Divitabs), slow release carbamazepine-D to Desitin carbamazepine (Timonil Retard), and slow release carbamazepine-F to Farmos Group Limited carbamazepine (Neurotol Slow). In a group of children selected because of their difficulty in controlling seizures, benefit was obtained in 36% on changing to slow release carbamazepine-CG. Half of six new patients treated with this preparation were also well controlled. The only other study that reports the clinical effectiveness of slow release carbamazepine found that 11 out of 18 children were improved by the use of slow release carbamazepine-D once daily (M Albani, B Sehringer-Mansour, unpublished observations); four of the patients became free of seizures and seven had diminished frequency of seizures. The outcome in six of the patients was not recorded, however, and in addition 13 of the 18 patients studied were taking several other drugs that were continued during treatment with slow release carbamazepine-D, so that it is impossible to assess fully the value of slow release carbamazepine-D in this study.

Some adult studies that reported no change in the frequency of seizures in patients who were changed to slow release carbamazepine-CG or slow release carbamazepine-F were too short to be valid.[11 12] One study showed complete control of seizures in 42% of adults changed from various anticonvulsant regimens to slow release carbamazepine-D, once daily, with reduced frequency of seizures in 16%.[13] Slow release carbamazepine-D seemed to be most effective in patients who had previously been receiving carbamazepine alone or in combination, and in patients affected only with tonic-clonic seizures. Our study of complex partial seizures was too small to differentiate response according to type of seizure.

Adverse side effects were observed in 30% of the children included in this study, but in most cases they were transient and tolerable so that it was necessary to discontinue treatment with slow release carbamazepine-CG in only two patients. Slow release carbamazepine-D has been reported to cause fewer side effects in children who had previously received carbamazepine alone or in combination (M Albani, B Sehringer-Mansour, unpublished observations), but some short studies in adult patients have reported no difference in side effects between treatment with standard carbamazepine and with slow release carbamazepine-CG and slow release carbamazepine-F.[13 14] Others have found that slow release carbamazepine-CG had a diminished effect on cognitive function compared with standard carbamazepine, although side effects still persisted in 17% of adult patients treated with slow release carbamazepine-CG.[13] Compared with standard carbamazepine preparations, however, slow release carbamazepine-F produced similar side effects,[14] and slow release carbamazepine-CG similar psychomotor function in healthy adult volunteers.[15]

In both children and adults cognitive function is impaired by higher serum concentrations of carbamazepine,[16 17] and other side effects are seen more often when blood concentrations of carbamazepine are above 36 μmol/l.[8 18] Using slow release carbamazepine-CG we were able to give higher doses with less risk of side effects than with the standard preparation. In six of our patients the doses were increased in excess of 30 mg/kg/day though none of these children experienced adverse side effects. Other authors have had similar experiences (M Albani, B Sehringer-Mansour, unpublished observations). This finding has important implications: the recommended dose range for slow release carbamazepine can be greater, with a maximum of about 30 mg/kg/day. Once the patient is on the higher dose of slow release carbamazepine he or she should not be changed automatically to the same dose of standard carbamazepine, as this could lead to adverse side effects.

As with standard carbamazepine, the time to achieve peak plasma concentration with slow release carbamazepine-CG was in the region of four hours. Similar observations have been reported for slow release carbamazepine-F,[12] D,[18] and CG.[16 19] The pharmacokinetic profile obtained using slow release carbamazepine-CG, however, was considerably smoother compared with the standard preparation (figure): the interdose variation was reduced by a factor of two by a 10% reduction in the mean peak carbamazepine plasma concentration combined with a 20–30% increase in mean trough concentration. The interdose variation found with slow release carbamazepine-CG in this study is comparable with results from previous studies using slow release carbamazepine-CG,[16] slow release carbamazepine-D,[18] and slow release carbamazepine-F[12] using twice daily doses. The degree of fluctuation, however, was reported to be much larger when slow release ca[illegible]pine-D was given once daily.[13] Reduced inte[illegible]dose variation in carbamazepine concentrations does not seem to be at the expense of bioavailability, as on slow release carbamazepine-CG twice daily the mean area under the carbamazepine concentration-time curve is not significantly different from the standard preparation (R Hartley, S W Ryan, I Forsythe, *et al*, unpublished observations); this is consistent with earlier reports.[11 16] The mean carbamazepine peak:trough plasma concentration ratio was 1·68 in children receiving standard carbamazepine, which was reduced by 24% to 1·27 using slow release carbamazepine-CG. The lower value (1·27) compares favourably with figures obtained with other preparations,[12 13 18] and indicates that slow release carbamazepine-CG has the characteristics of a slow release preparation.

Slow release carbamazepine seems to have several advantages over standard formulations, and should be considered in children with poorly controlled seizures. Some of the advantages could benefit new patients, as lower peak concentrations and reduced interdose fluctuations in plasma concentrations result in fewer of the adverse side effects (including impaired cognitive function). The same may apply to well controlled patients who have side effects. In addition, the pharmacokinetic profile of this preparation suggests the possibility of once daily dosage. For this to be effective the daily dose would probably have to be increased, and it would be advantageous to give the dose at night (2000) to benefit from the slower absorption observed at this time.[20] Night dosing would help to minimise adverse side effects (as the patient would be asleep) yet would ensure high plasma concentrations of carbamazepine during a period of high susceptibility to seizures (on waking). Adequate plasma concentrations would be maintained throughout the dose interval because of an appreciable increase in the apparent half life of carbamazepine in patients at steady state receiving slow release carbamazepine-CG (R Hartley, S W Ryan, I Forsythe, *et al*, unpublished observations). Once daily doses of slow release carbamazepine-D have been used successfully in children, mainly those receiving several drugs, but with a comparatively large fluctuation in blood concentration (M Albani, B Sehringer-Mansour, unpublished observations).

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Acute gastroenteritis in infants under 6 months old

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Abstract

Sixty two babies under the age of 6 months who were admitted with gastroenteritis completed a study of gradual refeeding compared with abrupt refeeding after a period of rehydration. There was no difference in the incidence of recurrence of diarrhoea due to lactose intolerance, effect on weight, or duration of hospital stay. Twenty six babies (42%) had recurrence of diarrhoea after refeeding, all of whom settled with the introduction of a lactose free soya based formula. Well nourished babies under 6 months of age with mild to moderately severe gastroenteritis can be fed immediately with full strength milk feeds after rehydration. The introduction of a lactose free soya based preparation may provide an alternative to repeated attempts at regrading with cows' milk feeds in those patients with lactose intolerance.

The dietary management of gastroenteritis in infants usually involves a period of starvation and oral or intravenous rehydration followed by gradual reintroduction of milk feeds, a system known as regrading. The principle argument in favour of regrading is the avoidance of the consequences of carbohydrate malabsorption.[1] Despite early clinical evidence that it is unnecessary[2] regrading has been seriously questioned only recently.[3–5] Early reintroduction of full strength feeds (rapid refeeding) is now recommended in patients over 6 months of age, but because data to provide guidance are unavailable, caution is still advised in younger infants.[6]

The use of standardised oral rehydration solutions is widespread in developing countries,[7] and in the United Kingdom where they are prescribed by general practitioners to 80% of infants with gastroenteritis.[8]

Carbohydrate malabsorption causes delayed recovery from acute gastroenteritis in infancy, especially in the malnourished[9] and in those who are very young.[10] Lactose intolerance is the most common presentation in children under the age of 6 months.[11] The incidence of lactose intolerance seems to be declining,[12] so therefore this study was designed to establish whether there is any advantage in gradually refeeding infants under the age of 6 months, with particular reference to (i) recurrence of diarrhoea and lactose intolerance, (ii) effect on weight, and (iii) duration of hospital stay.

Patients and methods

Sixty six babies under 6 months of age who were admitted to this unit with acute gastroenteritis (defined as acute onset of watery or extremely loose diarrhoea with or without vomiting for no more than seven days) were entered into the study between April 1988 and January 1989. Patients were excluded if the diagnosis was thought not to be gastroenteritis or if they were already receiving low lactose preparations for presumed lactose intolerance.

All babies received oral rehydration solution for 12 hours and were then randomly allocated to one of two feeding regimens. The solution used was Dioralyte (Rorer), which provides sodium 35 mmol/l, chloride 37 mmol/l, potassium 20 mmol/l, bicarbonate 18 mmol/l, and glucose 200 mmol/l. Group 1 were gradually refed with their usual cows' milk formula or breast milk at one quarter strength for 12 hours and then half strength for 12 hours, before commencing full strength feeds. Group 2 were immediately fed their usual full strength cows' milk formula or breast milk after a 12 hour period of oral rehydration. Nude weight was recorded on admission and daily thereafter, and percentage weight gain compared between the two groups. Stool frequency and consistency and the presence of blood and mucus were recorded by the nursing staff.

Recurrence of diarrhoea was defined as continued or return of diarrhoea with refeeding. Recurrence was presumed secondary to refeeding if no other cause could be established and lactose intolerance diagnosed if 0·5 to 2% reducing sugars were present in the stools when tested by Clinitest (Ames).[13] When recurrence was due to refeeding, the feed was changed to a soya based lactose free formula (Wysoy, Wyeth).

Specimens of the first three stools were cultured for pathogenic bacteria and stained for the presence of cryptosporidia. Viruses were identified (in the admission specimen) by tissue culture in monolayers of Hep 2 cells in addition to examination by electron microscopy after concentration by ultracentrifugation. Enzyme linked immunosorbent assay (ELISA) for rotavirus was not performed.

Informed parental consent was obtained in all cases. The significance of differences were calculated by the χ^2 and Mann-Whitney U tests.

Results

Four patients were subsequently excluded from the study (one patient had bilateral hydronephrosis, one patient had pyloric stenosis, and two patients were discharged by their parents against medical advice). Thus 32 patients in group 1, and 30 patients in group 2 completed

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the study. Characteristics of both groups are given in table 1. There were no significant differences in age, sex, ethnic origin, duration of symptoms, treatment before admission with oral rehydration solution, bottle compared with breast feeding, admission weight, stools in the first 24 hours, or average number of stools per day. All patients had mild or moderately severe gastroenteritis assessed by clinical signs of dehydration and none required intravenous fluids.

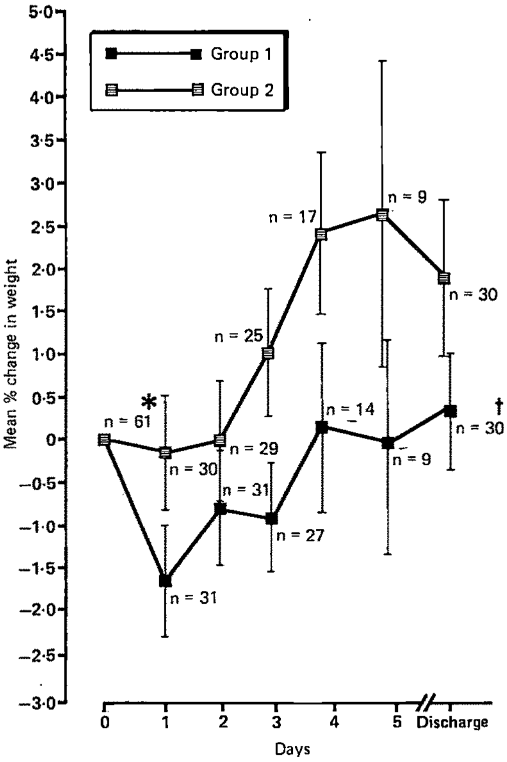
Table 1 Patient characteristics. Figures are given as mean (range)

	Group 1 (n=32)	*Group 2 (n=30)*
Age (weeks)	11·5 (2–22)	11·8 (2–24)
Sex M/F	11/21	12/18
Ethnic origin:		
White	26	22
Asian	5	7
Mixed	1	1
Duration of symptoms (days)	4·0 (1–7)	3·9 (1–7)
Prehospital treatment with oral rehydration solution (days)	21	22
Bottle/breast feeding	32/0	28/2
Admission weight (kg)	5·2 (3·0–8·6)	5·2 (3·1–7·3)
No of stools in first 24 hours	3·0 (0–8)	4·0 (0–7)
Average stools/day	2·4 (0·8–5·3)	2·9 (1·2–6·0)
Intravenous fluids required	0	0

There were no significant differences.

Table 2 Recurrence of diarrhoea within seven days of refeeding and treated with lactose free soya based formula. Figures are given as number (%)

	Group 1 (n=32)	*Group 2 (n=30)*	
Significant stool sugars (0·5–2·0%)	10 (31)	13 (43)	p>0·1 (χ^2=0·969)
No significant stool sugars	3 (9)	0	
No recurrence	19 (60)	17 (57)	p>0·5 (χ^2=0·048)



Mean % change in weight between the two groups. One patient in group 1 did not have admission weight recorded so was excluded; †another patient in group 1 did not have discharge weight recorded so was excluded. Vertical bars indicate 1 SEM. There were no significant differences between the groups.*

Twenty six patients (42%) had recurrence of diarrhoea within seven days of refeeding (table 2). They all settled satisfactorily with the introduction of lactose free soya based formula except one patient in group 2 who required an elemental feed (Pregestimil, Bristol-Myers) for a week before the diarrhoea stopped and lactose free soya based formula was reintroduced. Three patients in group 1 relapsed on refeeding without appreciable stool reducing sugars or evidence of other conditions leading to continued diarrhoea. On the basis of a satisfactory response to the lactose free soya based formula, two were presumed to have intolerance to cows' milk protein. The third patient was readmitted five days after refeeding, having been started on lactose free soya based formula 24 hours previously at home for presumed lactose intolerance. There was no significant difference in the incidence of lactose intolerance and no patient had recurrence of diarrhoea beyond seven days due to refeeding. There were no other factors associated with recurrence of diarrhoea such as age (less than 3 months), sex, ethnic origin, or treatment before admission with oral rehydration solution. Two other patients were readmitted with diarrhoea, one had a urinary tract infection and the other had a further episode of gastroenteritis due to rotavirus (no pathogen identified during first admission).

The figure shows the mean percentage weight gain of both groups from admission to day 5, and on discharge. Although group 1 tended to have greater initial weight loss this did not reach significance (Mann-Whitney U test) and both groups achieved satisfactory weight gain during their admission. All patients were above the third centile for weight.

The mean (SD) length of stay for group 1 was 4·3 (1·7) days and for group 2 was 4·2 (1·6) days. This was not significant, however; those patients who had a recurrence of diarrhoea remained in hospital for longer (5·2 (1·8) days, p<0·0001) than those who had no recurrence (3·6 (1·1) days).

Details of gut pathogens identified are shown in table 3. The commonest pathogens were rotavirus and adenovirus serotype 40 and 41. The viruses identified in the four other patients in group 1 were myxovirus, astrovirus, non-polio enterovirus, and Norwalk agent. There was no association between any particular aetiological agent and recurrence of diarrhoea or lactose intolerance, although the numbers were small.

Table 3 Pathogens

	Group 1 (n=32)	*Group 2 (n=30)*
No pathogen identified	18 (56%)	17 (57%)
Pathogen identified:	14 (44%)	13 (43%)
Rotavirus	4	5
Adenovirus	2	4
Calicivirus	2	0
Salmonella spp	1	2
Campylobacter	0	1
Adenovirus/salmonella	0	1
Escherichia coli	1	0
Other viruses	4	0

There were no long term complications and most patients placed on the lactose free soya based formula were successfully weaned back onto formula cows' milk feeds within six weeks.

Discussion

Previous studies have shown gradual reintroduction of cows' milk to be unnecessary in infants over 6 months of age with acute gastroenteritis.[3–5] A recent study came to the same conclusion in babies aged over 6 weeks.[14] Our study is the first to report on gradual refeeding compared with abrupt refeeding in all babies below 6 months of age.

Gastroenteritis in this country is usually of mild to moderate severity,[15] and our results show there is no advantage in gradually refeeding babies who present with mild to moderately severe gastroenteritis after rehydration. There is no difference in the effect on weight, duration of hospital stay, or recurrence of diarrhoea due to lactose intolerance. The incidence of lactose intolerance is high compared with previous studies[16] and rather surprising in view of the perceived decline of this condition in developed countries.[12] In a similar study by Dugdale *et al*,[4] however, in patients over 6 months of age, the incidence of recurrence of diarrhoea during admission or within seven days of discharge was 22% in a graduated refeeding group and 32% in an abrupt refeeding group. Trounce and Walker-Smith found an overall incidence of lactose intolerance of 7·5%,[11] but 73% of those patients were below 6 months so a higher incidence might be expected in this age group.

We have successfully treated lactose intolerance in our patients with a lactose free soya based formula thus confirming the efficacy of temporary omission of lactose from the diet.[16] Other authors have recommended repeated attempts at regrading with cows' milk feeds[11]; however, we would argue that this prolongs hospital stay unnecessarily when a simple, nutritionally adequate alternative is available.[17] The risk of developing soya protein intolerance at about 15% for children with cows' milk protein intolerance[18,19] or of aluminium toxicity in the presence of impaired renal function[20] would be the arguments against such an approach.

The overall incidence of identifiable pathogens in our patients is low, particularly rotavirus. In a study by Ellis and colleagues rotavirus was shown to be responsible for 35% of infantile gastroenteritis.[21] In addition, *Clostridium difficile* toxin was found in 4·9% of their patients. We did not routinely screen for *C difficile* toxin and the period of this study did not cover the peak of the rotavirus season, which occurs in the first four months of the year.[22]

Other studies have demonstrated an association between rotavirus infection and lactose intolerance,[11,16,23] a finding we did not confirm. As discussed above, however, the numbers in our study with rotavirus were particularly low.

We recommend rapid refeeding in well nourished well hydrated babies with acute gastroenteritis. The usual approach in our unit is to refeed with the patients' own cows' milk formula or breast milk wherever possible. Recurrence of diarrhoea due to lactose intolerance can be appropriately treated by a lactose free soya based feed and in view of the high incidence of lactose intolerance in our study it may be worth considering refeeding all hospitalised babies under 6 months with such a feed. This is an area worthy of further examination which should include a comparison of continuation of the same feed with a lactose free soya based formula.

See related articles on p 917 and p 939.

We gratefully acknowledge the assistance of Sister S Thompson and all nursing staff, ward 16, Monsall Hospital without whom this study would not have been possible. We also thank Dr V Hillier, department of medical computation, Manchester University Medical School for the statistical analysis.

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Management of gastroenteritis

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Abstract

Childhood gastroenteritis remains a common reason for admission to British paediatric units, although the severity of the disease appears to be diminishing in recent years. We studied 215 infants and children with gastroenteritis admitted consecutively to four paediatric units in South Wales in order to determine the severity of the disease, the organisms isolated, the frequency of complications, and the adequacy of management before admission. Stool pathogens were isolated in 125 (58%) patients (viruses in 65, bacteria in 30, and protozoa in 19, with multiple infection found in 11). There was a low incidence of morbidity and complications, but prolonged diarrhoea (postenteritis syndrome) was present in 24 (11%) cases and 77 (36%) had received inappropriate treatment before admission. Contemporary gastroenteritis is thus a relatively mild disease in the acute phase, but management before admission to hospital is often inadequate, and prolonged diarrhoea may be a feature in a considerable number of cases.

Infectious gastroenteritis is a common cause of morbidity in childhood and remains a major reason for admission to paediatric units in the United Kingdom. Ironside *et al* in 1967 showed that the disease was characterised by a significant incidence of complications, although in only 16% of cases was a pathogenic organism identifiable in the stool.[1] Since then, as a result of increased awareness and improved diagnostic techniques, several new pathogens have been identified and there have been important advances in the management of infant feeding and the use of oral rehydration therapy. A further study in 1984 from the same unit in Manchester suggested that the illness was milder than in the earlier series with a lower incidence of complications, and pathogenic organisms were identifiable in 75% of cases.[2] However, several deficiencies of care were highlighted in the phase of the illness before admission to hospital with, in particular, poor compliance with the recommended guidelines for fluid and dietary management of acute gastroenteritis.

A study in 1979 describing the experience of one unit in South Wales suggested a similar declining incidence of complications,[3] but no recent survey of contemporary gastroenteritis and its management has been reported from this geographical area. We thus undertook a prospective study of children with gastroenteritis admitted to four paediatric units in South Wales in order to determine the severity of the disease, the organisms involved, the incidence of complications, and also to assess the management of the disease before and during hospital admission.

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Patients and methods

All children admitted to four paediatric units in South Wales (three in South Glamorgan and one in Mid Glamorgan) with acute gastroenteritis were entered into a prospective study over 12 months, April 1987 to March 1988. The diagnosis of acute (infectious) gastroenteritis was based on the criteria of an acute diarrhoeal illness (at least five watery stools per day) with or without vomiting and no other evidence of extragastrointestinal infection or disease. Mothers were interviewed using a verbally administered questionnaire, which was completed by a senior clinician (usually one of the authors). Particular attention was paid to the management of the illness before admission and any treatment that had been recommended. Details of clinical examination were recorded and hospital treatment was left to the discretion of the admitting paediatric staff. Assessment of dehydration was based on generally accepted clinical criteria,[4] and a record was made of all laboratory results. Three separate stool samples were routinely examined and cultured for the presence of pathogenic bacteria, viruses, and parasites including giardia and cryptosporidia. The incidence of complications was noted and the clinical course of the illness recorded for each child, paying particular attention to the duration of diarrhoea and any changes in feeding management that were instituted in hospital before discharge.

Results

SOCIAL PROFILE AND CLINICAL FEATURES

During the study period 215 children (116 boys and 99 girls) had acute gastroenteritis diagnosed. The breakdown of results from the four units (all serving similar populations, both urban and rural) were very similar and results reported are from analysis of all 215 children. There was a male preponderance (54%) and the ethnic origin was white (206, 96%), Afro-Caribbean (seven, 3%), and Asian (two, 1%). The patients' age range was 2 weeks to 9 years with 130 (61%) children being less than 1 year old. A similar acute diarrhoeal illness present in first degree relatives was found in 37 (17%) admissions, and adverse family conditions (poor washing or sanitary conditions or overcrowding) as previously defined were found in 24 (11%).[2] Only 43 (20%) children had been breast fed for more than two weeks, and 170 (79%) patients were in or below social class III (manual), including unemployed (26, 12%) and single parents (15, 7%).

Serious dehydration was uncommon with only 15 (7%) being >5% dehydrated on clinical criteria. Intravenous rehydration, for a maximum of three days, was instituted in 26 (12%) children after assessment by middle grade paediatric staff with two children needing, in addition, prolonged parenteral nutrition. These two children, sisters aged 10 months and 20 months, were from a large, travelling family. Several pathogens were isolated from their stools and both developed severe protracted diarrhoea necessitating intravenous nutrition. All other children were treated with standard oral rehydration solutions and regraded according to recently published guidelines.[5] Other clinical abnormalities were present in a few patients. Thus fever of >38°C was found in 37 (17%), coryzal symptoms in 54 (25%), febrile convulsions in nine (4%), and rash in 13 (6%). Faecal blood and/or mucus was reported in 19 (9%) cases, with most (n=17) caused by bacterial infection. Fifteen children (7%) had a birth weight <3rd centile, although at the time of admission only nine (4%) were <3rd centile for weight. A previous episode of gastroenteritis was reported in 30 (14%) admissions. The duration of diarrhoea before admission was 1–15 days (median 4) with the total duration of symptoms from the start of the illness 2–29 days (median 7). Length of hospital admission varied from 1–43 days (median 4).

LABORATORY INVESTIGATIONS

Organisms were identified in the stools of 125 patients (58%) with virus alone in 65 (30%); of these rotavirus was found in 54. Bacteria alone were found in 30 (14%) (campylobacter (n=11), *Escherichia coli* (n=9), *Salmonella spp* (n=4), shigella (n=4), and aeromonas (n=2)) and parasites in 19 (9%) (cryptosporidia (n=13) and giardia (n=6)). Multiple infection with two or more organisms was present in 11 (5%) patients including two sisters with seven organisms each isolated from their faeces. These were the two children from a large family of travellers who required prolonged parenteral nutrition. Blood was taken for electrolytes and acid-base analysis in 76 patients (35% of total) on admission. The decision to perform these investigations was taken on clinical grounds by the paediatric registrars involved with the cases. Serum sodium concentration was <135 mmol/l (range 128–134) in 17 children and hypernatraemia (sodium concentration >145 mmol/l) was found in only two children (sodium 149 and 151 mmol/l). Urea concentration >6 mmol/l was present in 17 children (highest value 11) and bicarbonate <15 mmol/l in 13 children (lowest value 9).

MANAGEMENT BEFORE ADMISSION

A total of 204 children (95%) had previously been seen and treated by a general practitioner and 11 (5%) had been treated with a variety of remedies suggested by members of the family. Guidelines for the management of acute gastroenteritis have been published[5] and in only one of the group treated by the family and 137 of the group treated by the general practitioner could the treatment be termed appropriate. Appropriate treatment, for the infant and young child at least, consists of the cessation of milk and normal diet and the use of oral rehydration solution for a temporary period until the diarrhoea is resolving. In developed countries this is often only necessary for 24 hours and, indeed, there is current debate as to whether cessation of feeds is appropriate at all in many cases, particularly in the developing world where malnutrition is so prevalent. It is clear that drug treatment is not appropriate as a first line treatment, however, and antibiotics are indicated only in systemic illness after bacterial gut infection. Despite this, 49 (23%) patients in our study had received medication with a variety of drugs (see table) and 43 (20%) were not following the recommended guidelines for feeding during acute gastroenteritis.

COMPLICATIONS

Twenty six children (12%) required intravenous treatment with crystalloid solutions, usually because of continued vomiting, and two children (1%) required a prolonged period of intravenous nutrition because of protracted diarrhoea. In 24 (11%) cases overall a diagnosis of postenteritis syndrome was made, defined as continuing watery diarrhoea for more than seven days and three failed regrades. The method of regrading varied between the hospitals involved but generally consisted of a regime of increases in the strength of milk feeds offered to the child (quarter, half, three quarters, and full strength every 12 hours), and a failed regrade was defined as an increase in diarrhoea. The management decisions regarding feed changes were taken by the individual clinicians concerned. All but one of the children with postenteritis syndrome were <12 months old and there were no obvious factors before or after admission that distinguished them from the other study patients. Indeed, only the two children requiring parenteral nutrition were unwell and losing weight. After the institution of a cows' milk protein and lactose free diet using a specialised feed (8% soya milk, 2% protein hydrolysate, 1% comminuted chicken) the diarrhoea resolved. In all these children the

Treatment before hospital admission

	No (%) children
Treatment by general practitioner	204 (95)
Family remedy	11 (5)
'Inappropriate' management (total):*	77 (36)
Antibiotics	19 (9)
Kaolin and morphine	17 (8)
Antimotility agents	4 (2)
Metoclopramide	9 (4)
Continued milk feeds	39 (18)
Sugar and water	4 (2)

*Several children received more than one type of incorrect treatment.

exclusion diet was temporary (one to four months) and all are now on a normal diet.

Discussion

Our study of contemporary gastroenteritis in a South Wales population confirms that the illness is now relatively mild and free of complications. Hypernatraemic dehydration was previously a major complication of acute gastroenteritis in infancy and was linked to the administration of incorrectly reconstituted artificial milk feeds and the early introduction of mixed feeding.[1 2] Improved feeding practices contributed to the very low incidence of hypernatraemia found in the 1979 survey of gastroenteritis in South Wales.[3] It is gratifying to find in our study that hypernatraemia and severe dehydration are now rarities in children requiring admission to hospital. This is, in part, a tribute to the improved primary care in the community and the early use of appropriate oral rehydration solutions. Our study also highlights the fact, however, that the management of children before admission with acute diarrhoeal illness is often suboptimal and a significant number of patients had received inappropriate treatment before admission. This is particularly surprising as clear guidelines for the optimal management of childhood gastroenteritis have been published,[5] which recommended that drugs are rarely necessary, and may indeed be dangerous, in the early management of the uncomplicated case. Furthermore, it is disappointing that many of the children in our study were being fed inappropriately, and clearer guidelines need to be given to parents. Whatever the reason for the inappropriate management, it is obvious that treatment before admission of many of the children was inadequate and there is considerable scope for improvement both in terms of education and communication.

We were also surprised to discover that 11% of patients were changed to a specialised feed before discharge because of continuing diarrhoea and no weight gain over a period of seven days. All these children improved with the substitution of an appropriate exclusion diet. It is not possible to define accurately what proportion of these children suffered from dietary protein intolerance and how many suffered from lactose intolerance, as further investigations with jejunal biopsy and analysis of stool for reducing substances were not undertaken. Indeed, it may be that an exclusion diet was not, in fact, necessary in all these patients, but our study did not specifically address this point. Halliday *et al* have reported a similar high incidence (19%) of the postenteritis syndrome in an Australian population.[6] It is reassuring that the need for a specialised feed was temporary in all our patients and it is important that these children are followed up and challenged with cows' milk at an early stage (one to three months).

In summary, this study, which is the first comprehensive hospital based study of acute gastroenteritis in South Wales, has shown that the illness is relatively mild and the complication rate low when compared with previous studies. However, deficiencies in management before admission to hospital still exist and attention should be directed to improving education and, especially important, the communication between hospital and community care givers.

See related articles on p 917 and p 936.

We would like to thank the consultants involved for allowing us to study their patients and also Miss Leah Gallivan for typing the manuscript.

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Prognosis of chronic granulomatous disease

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Abstract

The records of 28 patients with chronic granulomatous disease born over a 32 year period were reviewed. The characteristics of the group, and the frequency with which various clinical and laboratory features had been recorded, was assessed. Nine patients were known to have died, in most cases of progressive suppurative infection. Actuarial analysis showed 50% survival through the third decade of life. The long term survival of patients developing symptoms after the end of the first year of life was significantly better than that of patients whose illness started in infancy. Our data confirm that the severity of chronic granulomatous disease is not uniform, and that the prognosis for long term survival is better than that suggested in earlier reports. Early onset may be a poor prognostic sign and invasive aspergillosis is a life threatening complication. In the absence of curative treatment, trials to assess the effectiveness of interferon gamma are necessary and early antenatal diagnosis should be offered to as many affected families as possible.

In 1957 Berendes, Bridges, and Good published a paper entitled 'A fatal granulomatosis of childhood. The clinical study of a new syndrome'.[1] Nine years later the same group showed that the syndrome was caused by an inborn inability of the patients' phagocytes to kill ingested microbes.[2] The salient features of lymphadenitis, superficial and deep abscesses, dermatitis, enlarged organs, and pneumonitis leading to chronic lung damage, were soon established.[3] Subsequent experience has shown that the condition is not universally fatal in childhood and that it affects predominantly, but not solely, boys.[4 5] The diagnosis is confirmed by performing the phorbol-myristate acetate stimulated nitroblue tetrazolium (NBT) test, which gives percentage values of stained neutrophils close to zero in affected cases, close to 100 in normal subjects, and intermediate (usually 20–80) in females heterozygous for the X linked form.

A defect of any one of the many potential sites in the metabolic pathways of the phagocytic respiratory burst could produce the chronic granulomatous disease phenotype and a number have been described. The commonest is a deficiency of a phagocyte cytochrome b seen in most cases of the more common X linked recessive form,[6] as a result of mutation in the gene for the larger β subunit of this haemoglycoprotein.[7 8] The gene has been mapped to the Xp21.1 region of the X chromosome and has been cloned.[9] Some patients with autosomal recessive, cytochrome b positive chronic granulomatous disease have an abnormality of one or a group of neutrophil cytoplasmic proteins, phosphorylation of which is thought to be concerned in the regulation of the oxidase mechanism of the respiratory burst.[10] This work has done much to increase the understanding of oxidative bactericidal mechanisms in normal phagocytes and provides a rational basis for the range of clinical severity seen in the chronic granulomatous disease phenotype.

No cure has yet been found for the disease. There has been a little experience with bone marrow transplantation and the results have shown at best partial success.[11–13] Palliation has been achieved with antimicrobial agents both as prophylaxis and for the treatment of infections as they occur. Retrospective studies have suggested that regular co-trimoxazole in particular improves the clinical course although no controlled prospective study has ever been done.[5 14] Antenatal diagnosis has only been made by carrying out the NBT test on fetal blood obtained at the late gestational age of 18–20 weeks.[15]

Important progress is now being made in all three of the areas of management mentioned above. Cure, in the form of somatic gene treatment, has not been achieved but is under investigation in several centres. Palliative treatment with interferon gamma is being studied; the cytokine has been shown in two small studies to ameliorate defective phagocyte function when given subcutaneously to some patients with both cytochrome b positive and cytochrome b negative chronic granulomatous disease.[16 17] Multicentre prospective controlled trials are currently in progress to assess whether the cytokine also confers clinical benefits. Finally, antenatal diagnosis by chorionic villous biopsy in the first trimester is now possible for the proportion of mothers that is informative for at least one of two polymorphisms within the X linked chronic granulomatous disease gene that have recently been described.[18 19]

This review was undertaken to record our clinical experience of this rare disease to date so that the information can be used as a guide in advising present and future patients and their families about the application of new interventions as they become available.

Methods

The records of our clinical immunology laboratory from 1964 to 1989 were reviewed and 38 patients were identified who had had abnormal

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NBT tests. Of these, 28 had been seen and followed up at our hospital and had adequate, traceable medical records; these formed the study group. All 28 had clinical histories suggestive of chronic granulomatous disease.

A proforma was designed to summarise demographic, clinical, family, laboratory, and follow up information and this was filled in from the hospital and laboratory records of each case. The data were analysed on a microcomputer, and Fisher's exact test was used to test the significance of differences between groups.

Results

DEMOGRAPHIC DATA

The patients were born over a 32 year period from 1955 to 1987. There were two sibling pairs, the remainder being unrelated. There were 26 boys and two girls. The racial pattern was predominantly white, reflecting that of our referral population.

ONSET AND DIAGNOSIS

The age at the onset of symptoms is shown in fig 1. In about half this was during the first year of life, and in 22 of 28 (79%) before the second birthday. The mean interval between onset and diagnosis fell with growing experience of the disease from 4·6 years in the 1960s to 1·5 years in the 1980s. Only two cases were diagnosed because they had positive family histories, both in the 1960s.

INHERITANCE (fig 2)

The two girls were presumed to have autosomal recessive inheritance. In both cases parental NBT tests were normal and one had confirmatory studies that showed a lack of phosphorylation of a 47 kDa cytoplasmic protein, but neither had affected siblings. Six boys whose mothers had normal NBT tests were designated 'autosomal or new mutation'. Seventeen boys whose mothers had abnormally low NBT test results were presumed to have X linked inheritance; six of these had pedigrees suggestive of this pattern. Two boys whose mothers had had abnormal bactericidal assays but no NBT tests done were designated 'probably X linked'; one of these also had a suggestive pedigree. One child had been adopted and no family data were available.

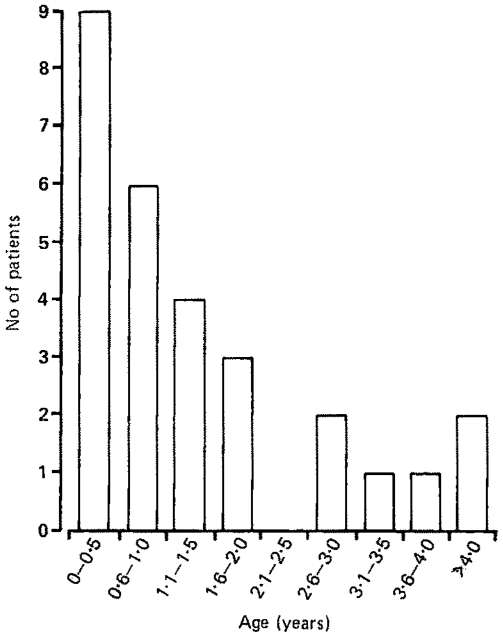

Figure 1 Age of onset of symptoms in 28 patients with chronic granulomatous disease.

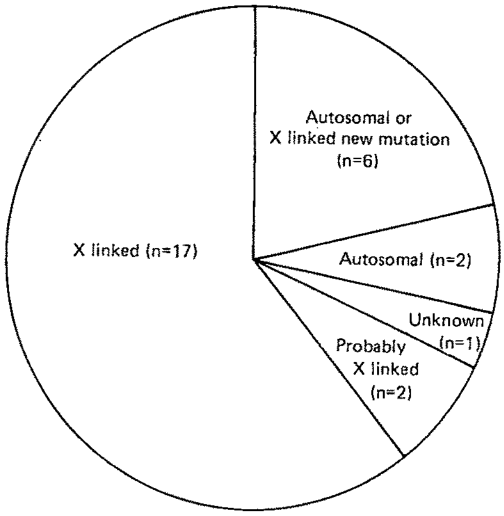

Figure 2 Inheritance pattern in 28 patients with chronic granulomatous disease.

CLINICAL AND LABORATORY FEATURES

The signs, symptoms, and complications recorded are summarised in table 1. Superficial abscesses, lymphadenitis and lymphadenopathy, recurrent fevers of unknown origin, chest infections, failure of growth, dermatitis, and enlarged organs were common features. A substantial minority developed invasive infection of bone, liver, or blood at some point. The recorded weights and heights at presentation were usually below the 50th centile and often low (fig 3). Nine of 24 patients (38%) were anaemic (haemoglobin concentration <100 g/l) and 11 of 20 (55%) were hypergammaglobuli-

Table 1 Clinical features recorded in 28 cases of chronic granulomatous disease. Figures are expressed as number (%) of patients

Common symptoms:	
Superficial abscesses and lymphadenitis	27 (96)
Persistent fever	20 (71)
Chest infections	17 (61)
Failure to thrive	15 (54)
Common signs:	
Lymphadenopathy	24 (86)
Dermatitis	23 (82)
Hepatomegaly	19 (68)
Respiratory signs	15 (54)
Splenomegaly	12 (43)
Uncommon features:	
Diarrhoea	5 (18)
Otitis	4 (14)
Gingivitis	3 (11)
Fungal nail infection	1 (4)
Aphthous ulcers	1 (4)
Invasive infections:	
Septicaemia	11 (39)
Osteomyelitis	10 (36)
Liver abscess	7 (25)
Brain abscess	2 (7)

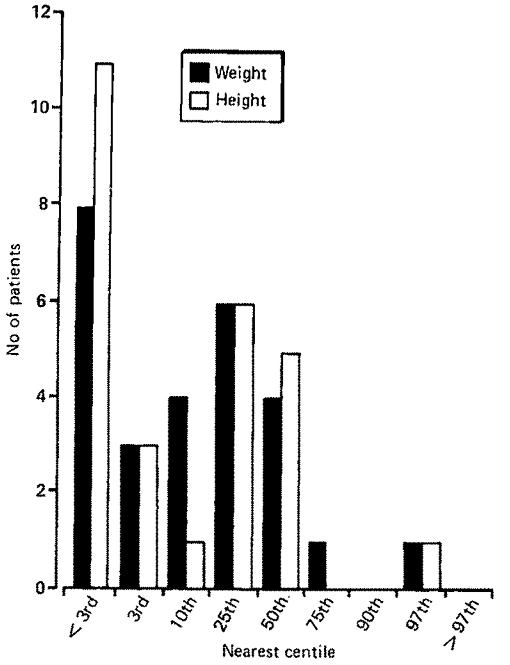

Figure 3 Nearest centiles at presentation in 27 patients with chronic granulomatous disease.

naemic at the time of presentation. In four families, a family history of systemic lupus erythematosus had been noted, and in two of these (and three others) the patients' mothers gave histories of photosensitive facial rash (discoid lupus).[20]

SURVIVAL

At the time of study, 16 patients were alive (five aged 0–9 years, five aged 10–19 years, and six aged 20–30 years, fig 4); nine had died, and three were lost to follow up. Six of the nine deaths were the result of progressive suppuration in the lung or other organs, or a combination. One patient died of liver failure after partial hepatectomy for a chronic liver abscess, one died during an exploratory laparotomy for intestinal obstruction, and one died of unknown cause having had bone marrow transplantation attempted seven years before. Most of the patients had received some form of antibiotic prophylaxis at some time, but there were inadequate data to correlate this with outcome.

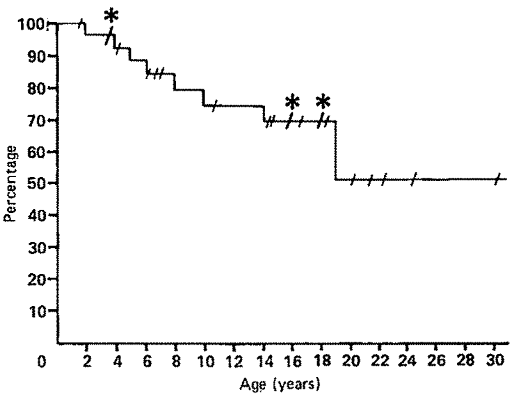

Figure 4 Actuarial survival curve for 28 patients with chronic granulomatous disease. Asterisks indicate a patient lost to follow up at that age.

Recent patients had consistently been given oral prophylaxis with co-trimoxazole.

Aspergillus infection occurred in eight patients. Three developed progressive infection of lung or bone, or both, and died; two of these received amphotericin. Two patients, one with an infected haematoma of the buttock and one with sternal osteomyelitis were still receiving treatment at the time of the study. Two patients, one with empyema and one with infection of the chest wall, were successfully treated. One patient was lost to follow up.

An actuarial survival curve was computed and is shown in fig 4. Six deaths occurred in the first decade of life and three in the second; six patients had survived into the third decade. There was more than 70% survival at 10 years of age, and 50% survival from 20 years of age onwards.

Discussion

As the clinical syndrome of chronic granulomatous disease is caused by a group of molecular disorders that lead to varying degrees of abnormality of phagocytic oxidative microbicidal function, it is to be expected that a range of clinical severity will be seen in patients with the disorder. Our experience certainly bears this out (fig 1, 3 and 4; table 1). A more mild clinical course among patients with the autosomal recessive cytochrome b positive type has been reported.[21] As in another recent report,[5] our series showed no apparent difference in clinical severity or mortality between the different inheritance groups (fig 2). We did not, however, have data on cytochrome b concentrations in our cases. It was of interest that the two female cases, who almost certainly have autosomal recessive type chronic granulomatous disease, both had illnesses of late onset (4 and 6 years), both are alive at the time of study (aged 7 and 22 years) and both have had relatively mild clinical courses with no growth failure, enlarged organs, or serious deep seated infection.

When patients who developed symptoms for the first time before their first birthday were compared with those who developed them later, a significant difference in the long term survival was found between the two groups (table 2). This suggests that onset in infancy may be an adverse prognostic indicator in chronic granulomatous disease.

Most previous reports have suggested a poor prospect of long term survival for children with chronic granulomatous disease,[3] although adults with the disease have been reported.[22]

Table 2 Long term survival correlated with age of onset in 17 patients with chronic granulomatous disease

	Alive and >14 years old	*Died before 14th birthday*
Onset before 1st birthday	2	6
Onset aged 1 or more	8	1
Totals	10	7

p=0·01.
The following were excluded: patients alive and <14 years old (n=6); those lost to follow up (n=3); and those who died after the age of 14 years (n=2).

One report of 48 paediatric patients showed a 50% survival rate maintained from 10 to 20 years of age.[5] Although there were some deaths in the second decade in our group, we have shown a similarly encouraging 50% survival rate extending into the third decade of life. The impression that chronic granulomatous disease is a 'less severe' disease now than when it was first recognised may in part reflect the use of prophylactic antibiotics and the diagnosis of less severely affected patients, but our data do show 50% long term survival rates among patients diagnosed in childhood more than 20 years ago.

Our patients were without exception troubled by recurrent or chronic symptoms, or both, and their lifestyles and those of their families were severely disrupted by the threat or occurrence of serious illness. The frequency of the various features and complications was comparable with that previously reported.[3–5] Although bacterial suppuration was the commonest infective problem, invasive infection with aspergillus carried a particularly high mortality when it occurred. The extreme difficulty of eradicating fungal infection in patients with chronic granulomatous disease, particularly when it affects the lungs or is disseminated, has previously been reported.[23]

In conclusion, this study confirms the main clinical features of chronic granulomatous disease, but suggests that there is reasonable hope of long term survival in paediatric cases. We intend to offer interferon gamma to patients with deep seated and unremitting infection, in particular that caused by *Aspergillus* spp. If current trials show that it is efficacious and safe, interferon gamma may also be offered prophylactically to patients who are well. Currently we offer first trimester antenatal diagnosis to known informative carriers of X linked chronic granulomatous disease, and second trimester diagnosis by fetal blood analysis to the remainder. Bone marrow transplantation is still a feasible therapeutic option if an HLA matched donor is available, but in time we hope that somatic gene treatment may become possible.

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Latent sensitisation to respiratory syncytial virus during acute bronchiolitis and lung function after recovery

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Abstract

To determine whether latent sensitivity to respiratory syncytial virus antigen(s) occurs after infection, 27 infants with acute bronchiolitis were studied and compared with 15 hospital controls. Blood was collected for whole blood challenge, and histamine release was measured by a high performance liquid chromatography technique with fluorometric detection. There was a significantly greater histamine release to respiratory syncytial virus antigen(s) in those with bronchiolitis than in controls, expressed either in amount (median 154 nmol/l compared with 104 nmol/l) or percentage release (median 20% compared with 3%). There was a significant difference between index and control groups in terms of individual histamine responses. These findings strongly suggest that infants develop latent sensitivity to respiratory syncytial virus antigen(s) during the course of acute bronchiolitis.

Serial lung function tests were performed in 15 infants. All infants had abnormalities of lung function at some stage, but the small numbers of subjects precluded comparison between 'sensitised' and 'non-sensitised' infants. Further study is indicated to define the relation of latent sensitisation and subsequent bronchial hyper-responsiveness after respiratory syncytial virus infection in infants.

Infections with respiratory syncytial virus occur in epidemics every winter in the United Kingdom, and are the main cause of acute bronchiolitis in infancy.[1] The virus is also associated with the sudden infant death syndrome (SIDS), which has a peak age range (2 to 6 months) similar to that of acute bronchiolitis.[2] Allergic sensitisation of the airways as a result of infection with respiratory syncytial virus has been postulated as an explanation for increased respiratory morbidity after apparent recovery from acute bronchiolitis,[3 4] and as a mechanism of death in some cases of SIDS.[5 6] The hypothesis of modified anaphylaxis as a cause of SIDS presupposes that mast cells and basophils are sensitised in some way by IgE and then release chemical mediators on subsequent exposure to specific allergens. Latent anaphylactic sensitivity of infants to allergens has been shown experimentally by assay of histamine release from blood on exposure to specific allergens—for example cows' milk proteins.[7]

The main aim of the present study was to find out whether latent sensitivity to respiratory syncytial virus antigen(s) occurs during the course of attacks of acute bronchiolitis in infancy, and whether there may be a relationship between latent sensitivity and lung function (including the responsiveness of airways to histamine) after apparent recovery from the acute illness.

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Patients and methods

LATENT SENSITIVITY

Patients

Twenty seven infants with bronchiolitis (mean age 17 weeks, range 3–42) were studied during the 1987/8 winter outbreak of respiratory syncytial virus infection. Fifteen infants (mean age 13 weeks, range 1–35), in hospital for non-respiratory illnesses, were studied as a control group. Six had been born after the end of the 1986/7 winter outbreak of respiratory syncytial virus infection and were studied before the onset of the 1987/8 outbreak.

The clinical details and course of the illness were carefully recorded for each index case. Nasopharyngeal aspirates were obtained so that viruses could be identified by indirect immunofluorescence and tissue culture. During venepuncture for routine clinical investigations an additional 2 ml venous blood was obtained for 'challenge' studies.

Challenge reagents

Goat antihuman IgE (E chain specific) was obtained from Sigma Chemicals (minimum titre 1:8).

Respiratory syncytial virus antigen consisted of respiratory syncytial virus strain A2 grown in Hep 2 cells with a standard 199 tissue culture medium containing added fetal calf serum proteins and antibiotics. The culture was centrifuged and the supernatant (containing respiratory syncytial virus antigen) collected for use in basophil challenges.

The control tissue culture (containing no respiratory syncytial virus) antigen consisted of uninfected Hep 2 cells grown in the same medium and then centrifuged, the supernatant being retained for use in the challenge test.

Pasteurised whole cows' milk was centrifuged at 8200 *g* for five minutes and the middle layer retained for use in the challenge studies.

Sample challenges

Venous blood was put in bottles containing lithium heparin and stored at 4°C. Preparation and challenge of the blood were carried out within three hours of collection to minimise histamine breakdown and extracellular histamine release from the basophils. After gentle mixing, the blood was divided into five 250 µl samples each of which was diluted with 250 µl phosphate buffered saline. Samples were then challenged with 50 µl of reagent and basophil histamine release was measured.

The individual sample challenges were:

- Goat antihuman IgE
- Respiratory syncytial virus antigen in tissue culture
- Control tissue culture (containing no respiratory syncytial virus)
- Pasteurised whole cows' milk
- Phosphate buffered saline (control).

Two infants who had been fed exclusively on breast milk had a sixth sample challenged with their mothers' breast milk.

The samples were agitated at 150 rpm and 37°C for 45 minutes to permit basophil histamine release to occur in response to the challenge, and then diluted with 250 µl of phosphate buffered saline and centrifuged at 3700 *g* for 10 minutes. The cell free supernatant was removed from each sample and the residual cellular component was made up to the same volume with phosphate buffered saline. Both the supernatant and the cellular components were deproteinised by the addition of an equal volume of 0·8 M perchloric acid. This was followed immediately by vortex mixing for one minute and incubation at room temperature for 30 minutes. The extracts were precipitated by centrifugation at 3700 *g* for 10 minutes. The supernatant containing histamine was then collected and diluted with an equal volume of distilled water, and the residues containing protein were discarded. A standard preparation of 250 µl of histamine hydrochloride 1 mmol/l was also taken through the assay.

Histamine assay

The samples were cleaned by passing them through a Sep-Pak C18 cartridge, and the histamine was measured by high performance liquid chromatography with fluorometric detection that permits measurement in nmol concentrations.[8] The histamine release was also expressed as a percentage of the total available histamine present in the basophils.[7]

Statistical analysis

The computerised Statistical Package for the Social Sciences was used. The data were not normally distributed, so non-parametric tests were used for analysis. The significance of differences was assessed by the Mann-Whitney U test, and the χ^2 test was used to compare differences between proportions.

FOLLOW UP ASSESSMENT OF LUNG FUNCTION

Fifteen of the original 27 infants admitted to hospital with acute bronchiolitis entered the follow up study. Their median age on admission to hospital was 11 weeks (range 4–21). None had pre-existing respiratory disorders or had been treated with mechanical ventilation during the course of the illness. Laboratory assessment of latent sensitivity was carried out at a median of six days (range 2–15) from the onset of the illness. The infants returned for clinical assessment and lung function tests at a mean (SD) of nine weeks (3 days) and 31 weeks (3 days), respectively, after discharge.

A standard protocol was followed for assessment of lung function. Each infant was sedated with chloral hydrate 100 mg/kg, and studied in an infant whole body plethysmograph (modified Jaeger) to measure thoracic gas volume and airways resistance. The infant (still asleep) was then placed in a polythene squeeze jacket with a face mask and pneumotachograph, and six or eight satisfactory partial expiratory flow volume (PEFV) curves were recorded to obtain a value for maximum flow at functional residual capacity ($\dot{V}$maxFRC).[9] A bronchial histamine challenge was then performed, provided that the infant had no clinical signs of lower airways obstruction; that the oxygen saturation measured by the Ohmeda Biox 3700 oximeter was greater than 90%; and that the PEFV curves were clearly distinguishable from tidal breathing curves at the end of expiration. Repeated inhalations of histamine phosphate were delivered by a Wright's nebuliser starting at a concentration of 0·25 g/l, and PEFV curves were repeated between each inhalation.[10] The challenge ended when a response to histamine occurred, judged by the shape of the PEFV curve. The procedure was stopped if the oxygen saturation fell below 90%. The dose of histamine necessary to produce a 30% fall in $\dot{V}$maxFRC was then calculated (provocative dose—PD_{30}). Details of the infant's clinical course after apparent recovery from bronchiolitis were noted.

Ethical approval

This study was approved by the Leicestershire Health Authority ethics committee. Informed consent was obtained from the parents of all infants after a thorough explanation of the nature of the study, and the tests and procedures to be undertaken.

Results

LATENT SENSITISATION

Comparability of the groups

There were significantly more boys in the control group than in the index group; no other differences were found (table 1).

Identification of viruses

Respiratory syncytial virus was identified from nasopharyngeal aspirates in 16 of the 27 infants in the index group. There were no significant differences in the clinical presentation or course of these infants when compared with those in whom respiratory syncytial virus was not identified (table 2).

Histamine release

When index and control groups are considered separately, neither age nor interval between onset of illness and blood sample had a significant effect on either total histamine release or on histamine release in response to the various challenges undertaken.

Within the bronchiolitis group no differences were observed between those infants who did and those who did not have respiratory syncytial virus isolated for any of the variables measured.

Table 1 Comparability of the groups

	Infants with bronchiolitis (n=27)	*Control infants (n=15)*
Mean (range) age (weeks)	17 (3–42)	13 (1–35)
Mean (SD) gestation (weeks)	38·7 (2·2)	39·6 (1·1)
Mean (SD) birthweight (g)	3170 (610)	3360 (580)
Male:female ratio	10:17*	13:2*
Feeding:		
Breast milk	5	2
Cows' milk	18	8
Both	4	5
Vomiting or possetting:		
None	18	5
Mild	5	3
Severe	4	7
Smoking:		
Mother	12	4
Father	12	9
Family history of atopic disorder	17	5

*$p<0{\cdot}05$.

Table 2 Clinical details of the 27 infants with bronchiolitis

	Infants in whom respiratory syncytial virus identified (n=16)	*Infants in whom virus not identified (n=11)*
Mean (SD) maximum respiratory rate/min	71·4 (14·4)	59·5 (15·6)
Mean (SD) maximum heart rate/min	164·1 (18·3)	154·1 (13·2)
Mean (SD) maximum temperature (°C)	37·8 (0·6)	37·5 (0·52)
No of infants receiving:		
Added oxygen	9 (range F_IO_2 30–85%)	4 (range F_IO_2 30–45%)
Ventilation	2	1
Intravenous fluids	5	1
No of infants with apnoeic episodes (>20 s)	1	2
Median (range) days in hospital	6 (3–15)	5 (1–14)
Median (range) days between onset of illness and venesection	6 (3–14)	5 (2–15)

F_IO_2=fractional inspired oxygen.

Thus the findings for the bronchiolitis group have been combined.

The results of the challenge tests for both groups of infants are given in table 3. Within the bronchiolitis group significantly more histamine was released on challenge with anti-IgE ($p<0{\cdot}0005$) and respiratory syncytial virus antigen ($p<0{\cdot}003$) than on the control challenge with phosphate buffered saline. No differences were observed among challenges with tissue culture medium containing no respiratory syncytial virus, cows' milk, and phosphate buffered saline. The response to challenge with anti-IgE antibody was significantly greater than either that to tissue culture containing no respiratory syncytial virus ($p<0{\cdot}003$) or that to cows' milk ($p<0{\cdot}02$). Histamine release to challenge with respiratory syncytial virus antigen(s) was greater than with respiratory syncytial virus culture medium, but this difference was not significant ($p<0{\cdot}09$). There were no significant differences within the control group. When the index and control groups were compared there was a significantly greater release of histamine in reponse to challenge with respiratory syncytial virus antigen among infants with bronchiolitis than among controls ($p<0{\cdot}05$).

The percentage histamine release in response to challenge in the index and control groups of infants is given in table 4. Within the bronchiolitis group the response to challenge with respiratory syncytial virus antigen was significantly greater than the responses to tissue culture containing no respiratory syncytial virus ($p<0{\cdot}003$) or to phosphate buffered saline ($p<0{\cdot}003$); among controls there was a significant difference between challenges with anti-IgE antibody and culture medium containing no respiratory syncytial virus ($p<0{\cdot}05$). The only significant difference between the two groups was in the response to challenge with respiratory syncytial virus antigen(s); this was significantly increased among infants with bronchiolitis ($p<0{\cdot}05$). There were no differences between the groups in response to challenge with cows' milk.

Table 3 Histamine release in response to challenge

	Infants with bronchiolitis (n=27)			*Control infants (n=15)*		
	Mean (nmol/l)	*Median (nmol/l)*	*IQR (nmol/l)*	*Mean (nmol/l)*	*Median (nmol/l)*	*IQR (nmol/l)*
Control (phosphate buffered saline)	106	104	61–146	93	97	23–130
IgE antibody	187	183	126–247	155	126	71–239
Respiratory syncytial virus antigen	172**	154	129–228	113**	104	14–192
Respiratory syncytial virus control	129*	130	78–189	90	84	33–147
Cows' milk	131	141	72–174	97	104	24–153
Total	478	395	235–678	454	365	264–568

*$p<0{\cdot}09$: difference between respiratory syncytial virus antigen and respiratory syncytial virus culture medium in bronchiolitis group. **$p<0{\cdot}05$: difference between respiratory syncytial virus antigen responses between bronchiolitis and control group of infants. IQR, interquartile range.

Table 4 Percentage histamine release in response to challenge

	Infants with bronchiolitis (n=27)			*Control infants (n=15)*		
	Mean (percent)	*Median (percent)*	*IQR (percent)*	*Mean (percent)*	*Median (percent)*	*IQR (percent)*
IgE antibody	23	24	11–34	20	14	0–27
Respiratory syncytial virus antigen	25**	20	6–33	12*	3	0–25
Respiratory syncytial virus control	10**	2	0–18	4	0	0–5
Cows' milk	18	5	0–17	6	0	0–13

*$p<0{\cdot}05$: difference between respiratory syncytial virus antigen responses between bronchiolitis and control groups of infants. **$p<0{\cdot}003$: difference between respiratory syncytial virus antigen and respiratory syncytial virus culture medium in bronchiolitis group. IQR, interquartile range.

Individual responses

After scrutiny of the distribution of responses of individual infants in the study groups, the release of 15% or more histamine was taken as a positive response to challenge. By this criterion, 20 of the 27 infants with bronchiolitis and five of the 15 controls had positive responses to respiratory syncytial virus antigen; the numbers for challenge with culture medium containing no respiratory syncytial virus were seven and one. A 10% cut off point gave similar results. A positive response to challenge with respiratory syncytial virus does not, therefore, necessarily indicate latent sensitisation to respiratory syncytial virus antigen(s). In seven infants in the bronchiolitis group, and one in the control group, the results were 'uninformative' in that positive results were obtained from challenges both with respiratory syncytial virus antigen(s) and with the culture medium containing no respiratory syncytial virus. Table 5 shows the individual responses taking this into account; there was a significant difference between the bronchiolitis and control group ($\chi^2=6{\cdot}93$; $p<0{\cdot}01$). Further examination of 'uninformative' data indicated that the difference in percentage release of histamine between challenge with respiratory syncytial virus antigen and with tissue culture containing no respiratory syncytial virus exceeded 15% in a further three infants with bronchiolitis and one control infant. Adjusting the results given in table 5 to include these infants as positive responders to respiratory syncytial virus antigen(s) does not alter the significance of the original analysis.

There was a wide range of response to cows' milk challenge. Six of 23 infants investigated in the index group showed a response of 15% or more, compared with three of 13 control infants. All six who responded to cows' milk in the index group also responded to respiratory syncytial virus antigens, and four responded to culture medium containing no respiratory syncytial virus. There was, however, concordance of responses between cows' milk and culture medium containing no respiratory syncytial virus in 19 of the 23 infants studied. In the control group, three who responded to cows' milk also responded to respiratory syncytial virus antigen(s), and one responded to culture medium containing no respiratory syncytial virus. There was concordance of response between milk and culture medium containing no respiratory syncytial virus in 11 of 13 infants studied.

Table 5 Individual responses to challenge with respiratory syncytial virus antigen(s)

	Infants with bronchiolitis (n=27)	*Control infants (n=15)*
Response to antigen >15%, response to culture <15%	13 (16)	4 (5)
Response to both antigen and culture >15% ('uninformative')	7 (4)	1
Response to both antigen and culture <15%	7	10

Figures in parentheses include those infants in whom antigen and virus free culture histamine release were >15%.

Clinical aspects

Seventeen cases and five control infants had family histories of asthma or atopic disorders in first degree relatives. This did not influence their response to any of the challenges undertaken. Four infants in the bronchiolitis group and two control infants were breast fed (without additional milk) at the time of testing. Three of these six infants gave positive responses to challenge with cows' milk. Of two infants fed exclusively on breast milk one responded equally to challenges with breast milk and cows' milk, and the other to neither challenge.

LUNG FUNCTION

The results of tests of latent sensitivity and lung function for the 15 children studied are shown in table 6. Eleven had developed latent sensitivity during their acute illnesses. Two (cases 14 and 15) were readmitted to hospital before the first set of lung function measurements with severe respiratory infections (attributed to adenovirus, type unknown); they continued to have symptoms throughout the period of study. Of the remaining 13 infants, two showed hyperinflation (thoracic gas volume >120% predicted) and five had raised airways resistance (>140% predicted) at the first test. All infants had substantially reduced $\dot{V}$maxFRC values, and only four fulfilled the criteria for inhalational histamine challenge (mean (SD) $PD_{30}=0{\cdot}4\ (0{\cdot}2)$ g/l).

Table 6 Details of results of latent sensitisation and lung function in 15 infants

Case No	*Duration of admission (days)*	*Infant sensitised*	*Thoracic gas volume (% of predicted)*		*Airways resistance (% of predicted)*		*$\dot{V}$maxFRC (% of predicted)*		*Provocative dose$_{30}$ (g/l)*		*Symptoms present between discharge and time of last lung function test*
			Test 1	*Test 2*	*Test 1*	*Test 2*	*Test 1*	*Test 2*	*Test 1*	*Test 2*	
1	3	Yes	124	89	88	87	18	30	0·25	0·25	No
2	11	No	107	78	187	80	Tidal	13	Not done	Not done	Yes
3	5	Not known	71	74	197	100	Tidal	8	Not done	Not done	Yes
4	2	No	100	106	71	66	27	27	Not done	0·3	Yes
5	2	Yes	90	77	90	93	Not done	16	Not done	1	Yes
6	5	Not known	71	72	61	60	18	24	Not done	0·25	No
7	7	Yes	97	106	85	100	32	39	0·25	1·28	No
8	1	Yes	72	79	100	75	23	59	0·43	1·4	No
9	3	Yes	126	126	147	236	Tidal	Tidal	Not done	Not done	Yes
10	5	Yes	74	75	100	90	18	39	Not done	0·33	Yes
11	6	Yes	92	89	144	142	12	13	Not done	Not done	Yes
12	8	Yes	105	85	196	168	27	45	Not done	0·25	Yes
13	6	Yes	77	85	134	123	60	37	0·67	0·48	Yes
14	3	Yes	Not recordable		Not recordable		Tidal	Tidal	Not done	Not done	Yes
15	9	Yes	Not recordable		Not recordable		Tidal	Tidal	Not done	Not done	Yes

Case 14 and 15 subsequently became infected with adenovirus.

At the second test, eight months after the original illness, eight infants showed functional improvement. One remained hyperinflated and three had raised airways resistance. The median V̇maxFRC had increased from 18 to 27% predicted. Nine infants fulfilled the criteria for histamine challenge (mean (SD) $PD_{30}=0{\cdot}62$ (0·47) g/l). Severity of lung dysfunction in terms of overall mechanical properties was not associated with latent sensitisation during the acute illness, clinical severity of the acute bronchiolitis, duration of hospital stay, or the frequency and severity of symptoms that developed after discharge from hospital.

Paired data on responsiveness to inhaled histamine challenge was obtained for only four infants—all of whom were 'sensitised' to respiratory syncytial virus allergen(s). Paucity of data on 'non-sensitised' or uninformative cases does not permit comparison of 'sensitised' and 'non-sensitised' infants.

Discussion

LATENT SENSITISATION

The basophil histamine release system is an established laboratory model of the anaphylactic reaction.[11] Assays can be carried out either in whole blood or in a preparation of washed white cells. Histamine release from whole blood was chosen for this study, as this system is more physiological and retains full viability and reactivity of the basophils. Basophil histamine release detects sensitisation of basophil by IgE antibodies specific to the allergen—in this case respiratory syncytial virus—and may be more sensitive than estimation of allergen specific circulating IgE, particularly if total IgE concentrations are low.

IgE mediated histamine release from basophils or whole blood may be influenced by many factors including age, allergic disease, and viral infection. The index and control groups were comparable with respect to age, allergic disease background, and total serum IgE and IgG_4 concentrations. Interference from non-immune mechanisms of histamine release was minimised by using isotonic solutions when preparing the blood, and avoiding mechanical trauma to the basophils. None of the subjects had been given drugs that are known to release histamine. As we were interested in sensitisation to viral antigen(s), the time interval between infection and sampling was clearly important. There was, however, no correlation between the interval between the onset of illness and the time of taking the blood samples (median six days), and the total basophil histamine concentration or the release of histamine in response to the various challenges.

Histamine release is generally expressed as a percentage of the total histamine concentration. This is not an entirely satisfactory way to express the results of challenges in infants with low total histamine concentrations as a difference in histamine release, expressed in nmol/l, that is less than that caused by the variability of the method could produce a misleadingly large percentage histamine release. For this reason we have presented both actual histamine concentrations and the percentage of histamine released.

Ethical constraints meant that venous blood samples were often taken before virological identification was complete. Respiratory syncytial virus was identified in 16 of the 27 infants with clinical bronchiolitis (59%), which compares favourably with a reported sensitivity of immunofluorescence under ideal circumstances of 70%.[12] The subgroup of infants in whom the virus was identified tended to have more severe acute illnesses, although individual indices of severity were not significant (table 2). Severity of illness is related to viral shedding in the respiratory tract and may account for the ease with which viruses could be identified.[13] Infants in hospital with non-respiratory disorders were selected as the control group, the preponderance of boys being partly explained by the fact that several had congenital hypertrophic pyloric stenosis.

There is a wide range in whole blood histamine concentration in infancy and that reported in this study of 107–1251 nmol/l (equivalent to 22–230 ng/ml) is higher than the range reported previously by McLaughlan and Coombs of 12–128 ng/ml.[7] The histamine release to anti-IgE was variable, and nine subjects (33%) showed <15% response to this challenge. Limitations in the size of the blood samples meant that challenges were made at only one concentration of anti-IgE, which may not have produced optimal release of histamine in each case. Our results are comparable with those of McLaughlan and Coombs, however, who reported that only 17% of the group showed no response to IgE antibody.[7]

Our results suggest that latent sensitivity to respiratory syncytial virus antigen(s) occurs during the course of infection with respiratory syncytial virus (tables 3 and 5). Both the within group and between group comparisons suggest that challenge with respiratory syncytial virus antigen has a significant effect on release of histamine from whole blood. Among individual infants 13 with bronchiolitis and four controls were considered respiratory syncytial virus 'responders' from their percentage release of histamine (>15%). The figure indicating a significant percentage release of histamine, however, varies among published reports, McLaughlan chose 9% on the basis of an adult control population[7]; others have used 30% or >50% of that produced by the optimal IgE concentration.[14 11] We cannot explain the variations in responsiveness among infants in the bronchiolitis group, and have no information about whether interferon production or respiratory syncytial virus subtype influenced the results.[15]

The uncritical assumption that our results indicate allergic sensitisation to respiratory syncytial virus antigen(s) is not warranted. We did not include a 'control' virus challenge in our study design so that a non-specific viral effect cannot be excluded, although any such effect would have affected index and control groups of infants similarly. Perhaps of greater relevance is the finding of positive responses to challenge with culture medium containing no respiratory syncytial virus within both groups. This may be explained by the fact that the culture medium contained fetal calf serum proteins; it is for that reason that a cows' milk challenge was included in the study protocol. Parallel patterns of response to culture medium containing no respiratory syncytial virus, and to cows' milk, within both the index and control groups, suggests that 'sensitisation' to cows' milk proteins is an important confounding factor that could affect the interpretation of the results of challenge with respiratory syncytial virus antigen. The analysis given in table 5 tries to overcome this problem. The significant difference shown between the index and control groups may, however, have been caused as much by the distribution of 'uninformative' data as by any real difference in responsiveness to respiratory syncytial virus antigen(s).

'Sensitivity' to respiratory syncytial virus antigens was observed in five control infants with no previous history of respiratory illness. This finding may be spurious, as sensitisation to cows' milk protein would explain it in three infants. Previous sub-clinical respiratory syncytial virus infection cannot be excluded, however, in the remaining two in whom there was no response to challenge with cows' milk. It is of interest that five of the six infants born between seasonal epidemics of respiratory syncytial virus infection showed no response to either respiratory syncytial virus antigen or to cows' milk challenges; the remaining infant showed 'sensitisation' to both.

In their original paper on latent anaphylactic sensitisation to cows' milk protein, McLaughlan and Coombs extrapolated from data on normal adults and chose a 9% level of histamine release to indicate a degree of latent sensitivity. They reported that a quarter of their infants responded at this level, with roughly 10% releasing more histamine (15–63%). The data on cows' milk from our infants (bronchiolitis and controls, n=37) correspond with 12 infants showing >9% histamine release, nine infants showing >15% release, and five infants showing >20% release. The lack of concordance between the response to the respiratory syncytial virus antigen and milk among the infants studied lends support to the notion that independent immunological reactions are occurring.

We did not measure antirespiratory syncytial virus IgE either during the acute illness or at follow up in any of the infants studied. Published reports of the detection of antirespiratory syncytial virus IgE some weeks after respiratory syncytial virus bronchiolitis, however, lend support to the interpretation of the present results—that allergic sensitisation to respiratory syncytial virus antigens occurs during the course of acute bronchiolitis.[16 17]

A great deal is now known about the immune response to respiratory syncytial virus infection but its role in the pathogenesis and protection against infection has yet to be fully clarified. Current knowledge in this area has been recently reviewed.[18] The finding of antirespiratory syncytial virus specific IgE in nasopharyngeal secretions after respiratory syncytial virus infection is of most interest in the context of the present study. A systemic cell mediated response has also been described.[19 20] There is, however, a growing suspicion that defective regulation of immune responses to respiratory syncytial virus infection is an important determinant in the outcome of the infection.[21]

Confirmation of latent sensitivity to respiratory syncytial virus infection indicates that there is a potential for clinical type I responses on re-exposure to antigen(s). Mast cells, like basophils, express high affinity surface IgE receptors and despite a number of important differences between the two cell types they are often considered functionally analagous.[22] If mast cells in the airways react like circulating basophils in response to viral antigen(s) the scene is then set for local release of histamine in the airways on repeated exposure to respiratory syncytial virus. Neither the time course of acquisition nor the duration of latent sensitivity to respiratory syncytial virus infection is known, and its association with respiratory outcome is speculative.

LATENT SENSITIVITY AND SUBSEQUENT LUNG FUNCTION

These data confirm reports of abnormalities in lung function during the months after recovery from acute bronchiolitis.[23] Hyperinflation was much less common than at least one recent report suggests,[24] the result perhaps of improvements in methods.[25] The introduction of the technique for recording partial expiratory flow volume curves in infancy gives additional information. A decrease in VmaxFRC values immediately after an attack of bronchiolitis with a return to normal after six months has been reported in infants with mild bronchiolitis who were not admitted to hospital.[26] Our results, in infants in hospital, show that severe limitation of airflow can persist for at least eight months after the acute illness, even in infants who are free of symptoms.

A technique for carrying out inhalational challenge studies in infants has recently been described.[10] Normal data in infancy are scanty but Le Souef *et al* reported a range for PD_{30} to histamine of 0·3–5·1 g/l (geometric mean 1·4 g/l) in 12 apparently normal infants at a mean age of 7·8 months.[27] The infants that we studied come at the lower end of this range. Tepper *et al* have recently reported that infants with a history of bronchiolitis have heightened airway reactivity to methacholine when compared with controls.[28] One of the original aims in this study—paired histamine challenges for each infant during the nine months after an attack of acute bronchiolitis—proved impossible, as the unexpected severity of airways dysfunction limited the histamine challenge to only four infants at the first test, and to nine infants eight months after their original illness.

The interpretation of the results of lung function tests in the follow up of acute bronchiolitis may be confounded by the effects of other respiratory viruses that the infants encounter in the interim period. Two of our original cases acquired adenovirus infections that could have accounted for the severe clinical symptoms and abnormalities of lung function that we observed. Most other infants reported 'colds' during the nine month study period and some may have been reinfected with respiratory syncytial virus. Although we identified the infants who developed latent 'sensitivity' during attacks of acute bronchiolitis, we have no information on how long it lasts or how it is affected by subsequent respiratory syncytial virus infection.

Although allergic sensitisation of the airways may be a factor that contributes to morbidity after respiratory viral infection, there are other postulated mechanisms for airway injury or infection, or both, which could mask the effect of any single factor. The apparent similarity of respiratory outcome for 'sensitised' and 'non-sensitised' infants studied over a relatively short period of time does not necessarily preclude a 'sensitising' role for respiratory syncytial virus infection that contributes both to pulmonary dysfunction and hyper-responsiveness of airways after attacks of acute bronchiolitis. Systemic sensitisation has previously been connected with airways hyper-responsiveness of airways in adult asthmatic patients.[30]

CONCLUSION

The results of antigen challenge in infants with bronchiolitis and a group of control infants suggest that latent sensitivity to respiratory syncytial virus infection occurs during the course of attacks of bronchiolitis. Further studies are indicated to confirm this, including a controlled virus challenge and challenges with individual purified components of respiratory syncytial virus that may be of importance in the pathogenesis—for example, glycoproteins F and G, and measurements of antirespiratory syncytial virus IgE after infection.[31] Further studies should also take account of the respiratory syncytial virus subtype. Ideally, future follow up assessments of lung function should include a measure of 'sensitivity' at the time of testing.

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Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death

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Abstract

The pathophysiology of recurrent cyanotic episodes has been investigated in 51 infants and children. Episodes began at a median age of 7 weeks (range 1 day to 22 months, 39 at less than 4 months). They were characterised by the rapidity of onset and progression of severe hypoxaemia with early loss of consciousness from cerebral hypoxia. The most common precipitating factor was a sudden naturally occurring stimulus from pain, fear, or anger. In uncontrolled trials, cyanotic episodes were reduced in frequency and severity by tetrabenazine (n=15) and additional inspired oxygen (n=10). Eight patients died suddenly and unexpectedly (four during cyanotic episodes). Twenty eight patients underwent physiological studies during cyanotic episodes. There was no evidence of seizure activity at the onset and although prolonged absence of inspiratory effort with continued expiratory efforts was common, breathing sometimes continued. Episodes were not caused by upper airway obstruction and sometimes occurred during positive airway pressure ventilation. The rapidity of fall in arterial oxygen pressure and continued breathing suggested a right to left shunt of sudden onset. The results of contrast echocardiography and lung imaging studies confirmed that this was occurring within the lungs.

These cyanotic episodes included both intrapulmonary shunting and prolonged expiratory apnoea. They are best explained by interactions between central sympathetic activity, brainstem control of respiration and vasomotor activity, reflexes arising from around and within the respiratory tract, and the matching of ventilation to perfusion in the lungs. They are a cause of sudden unexpected death in infancy and early childhood.

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In preliminary communications we have described our investigations of infants and young children presenting with cyanotic episodes.[1–4] These episodes were characterised by the rapid onset and progression of severe arterial hypoxaemia that was not caused by airway obstruction or seizures. Possible mechanisms included the rapid utilisation of reduced oxygen stores created by prolonged expiratory apnoea at low lung volumes, or the sudden development of areas of atelectasis resulting in a mismatch between ventilation and perfusion. Recent observations that severe hypoxaemia may develop rapidly despite continued spontaneous or mechanical ventilation have lead to further investigations. These, and the observations made from trials of treatment, have helped provide a better understanding of their pathophysiology.

Patients and methods

Fifty one infants and young children with recurrent episodes of cyanosis including loss of consciousness were studied. Thirty nine (76%) patients were otherwise healthy, and the remaining 12 had associated defects and congenital anomalies (table 1). The age range for the onset of the cyanotic episodes was 1 day to 22 months (median 7 weeks). Thirteen were 7 days old or less, 24 were 6 weeks old or less, and 39 were 4 months old or less at the time of their first episode. The range of birth weights was 1650–4280 g (median 3130 g). Four were born prematurely (case 18 at 36 weeks, 21 at 33 weeks, 25 at 34 weeks, and 29 at 31 weeks). A family history of cyanotic breath holding episodes in parents or siblings, or both was elicited in 24 (47%) and was unknown in three cases. Clinical assessment elicited no evidence of congenital heart lesions, upper airway obstruction, or lung parenchymal disorders.

In all 51 patients most of the cyanotic episodes began when the child was awake, usually after a naturally occurring stimulus such as pain, fear, or anger resulting in a cry or an attempt to cry. The stimulus was more often a sudden shock (with an 'element of surprise' or 'unexpectedness') rather than a gradually increasing provocation.[5] This presentation is

Table 1 Clinical details and case numbers

Clinical details	*No of children*	*Case No*
Otherwise healthy children	39	4–6, 9–14, 16–20, 23 26–37, 39–41, 43–51
Brainstem abnormalities:		
Meningomyelocele, Arnold-Chiari malformation	3	22, 24, 25
Developmental anomaly at pontomedullary junction	1	8
Medullary glioma	1	38
Brainstem disorder of unknown origin	1	2
Congenital alveolar hypoventilation	1	1
Primary sensory dysmyelination	1	42
Repaired tracheo-oesophageal fistula	3	3, 7, 21
Repaired vascular ring (and monosomy 9p)	1	15
Total	51	

identical to that described as 'cyanotic breath-holding'.[5] Episodes were more common when the patient was tired, when there was a high level of emotional tension in the home, or when the routine of the child was interrupted. The occurrence of a cyanotic episode seemed to create a vulnerable 10 minute period in which further episodes were more likely to occur. Infection, particularly respiratory, increased the frequency and severity of cyanotic events. In almost all cases parents spontaneously voiced their concern that their child might die during one of these events. Episodes commonly began with a series of expiratory cries without inspiratory efforts, often with a widely opened mouth. Sometimes an episode began with a single prolonged cry that was silent, the expiratory apnoea beginning immediately. If crying became established without prolonged apnoea or cyanosis, then an episode was unlikely to occur or be induced.

In six patients hypoxaemic episodes also began in other circumstances. In cases 8, 22, 24, and 25 (all of whom had brainstem anomalies) a smaller proportion of episodes (25%) occurred when quietly awake, when feeding, and when asleep. In cases 3, 7, and 21, who had undergone repair of tracheo-oesophageal fistulas, around 10%, 60%, and 90%, respectively, of their episodes were brought on by swallowing. Characteristically the patient would be eating solid food, some of which would seem to stick in the oesophagus. An attempt to cry would follow, then respiratory efforts would cease, and severe hypoxaemia would rapidly develop.

INVESTIGATIONS DURING CYANOTIC EPISODES

Because of their unpredictability only 28 patients underwent physiological recordings *during* cyanotic episodes. The remaining 23 had episodes with characteristic histories and clinical observations, and this suggested that the same underlying pathophysiology was operating. In the 28 cases investigated during episodes it was difficult to obtain optimal physiological data because of the need to institute resuscitative measures. Investigations were only performed with the fully informed consent of parents.

Radial artery samples were taken for measurement of oxygen pressure (PaO_2), carbon dioxide pressure ($PaCO_2$), and pH and the time from the onset of apnoea was noted in cases 2, 5, 8, 9, 18, 36, 50, and 51. Measurements were only documented when prolonged expiratory apnoea and cyanosis followed immediately after the initial attempt to cry.

Contrast echocardiograms were taken using an intravenous injection of micro air bubbles in 5% dextrose in cases 2, 5, 9, 10, 18, and 22.

Tape recordings (Racal Store 4) of the following signals were made in various combinations (n=28): (i) beat by beat oxygen saturation (median total response time 4 seconds) from a pulse oximeter (Nellcor N100 or N200) including the analogue signal representing each plethysmographic waveform used to derive the saturation in order to identify artefact (n=28)[5]; (ii) ribcage and abdominal movements from respiratory inductance plethysmography (Studley Data Systems) or from magnetometers or pressure capsules (n=28); (iii) electrocardiograms (n=28); (iv) airflow from a thermistor (Yellow Springs Instrument Co) or from expired carbon dioxide sampling (Engstrom Eliza) (n=28); (v) oesophageal pressure from a balloon catheter (PK Morgan) placed to detect both negative pressure changes with inspiration and cardiac artefact in cases 2–4, 10, and 18; (vi) electromyogram from the external oblique muscle in cases 2, 3, 4, 10, and 18); (vii) airflow integrated to volume using a facemask and pneumotachograph (Fleisch 00) in cases 2, 10, 18, and 22; (viii) arterial blood pressure from a radial artery line and Medex pressure transducer in cases 2 and 18; and (ix) pulmonary artery pressure (from an indwelling Swann Gantz catheter and Medex pressure transducer) in 22 hypoxaemic episodes in cases 10 and 18.

Chest fluoroscopy or chest radiographs were undertaken in cases 2, 8, 10, 18, and 22.

Electroencephalographic 8–12 channel recordings were made in cases 2–11, 13, 17, 18, 22–25, and 38.

Krypton-81m inhalation dynamic ventilation scans (cases 2 and 10) and krypton-81m infusion scans were done in patients 8, 10, 22, 30, and 46. Dextrose 5% was passed through a rubidium-81m column using an infusion pump, thus producing krypton-81m in solution. This solution was then infused continuously at a rate of between 6 and 10 ml/minute into a venous cannula in the hand. On reaching the lungs all the krypton crosses the alveolar to capillary membrane, thereby producing a scan of both lung fields. A shunt within the lungs results in ^{81m}Kr appearing in the systemic circulation and being detected outside the lung fields. During these scans a record of oxygen saturation was made at two second intervals.

Fibreoptic nasendoscopy was carried out under light general anaesthetic in cases 2, 3, 7, and 18.

The effects of breathing 15% oxygen (balance nitrogen) while awake and 18% oxygen (balance nitrogen) while asleep were investigated in case 10.

INVESTIGATIONS BETWEEN CYANOTIC EPISODES

Thirty two patients underwent overnight (roughly 12 hour) tape recordings of oxygen saturation, breathing movements, nasal airflow, and electrocardiography using the techniques described above.

Cases 3 and 32, at the ages of 7 and 9 years, respectively, underwent tape recordings of oxygen saturation, breathing movements, and nasal airflow before and during voluntary end expiratory breath holding for as long as they were able to, with nasal and oral airways occluded.

CONTROLS AND THEIR INVESTIGATIONS

Overnight tape recordings were compared with similar data collected from randomly selected healthy infants or children (40 in the neonatal period, 67 in the second month, 20 in the third,

Table 2 Radial artery blood gas measurements during cyanotic episodes

Case No	*Before cyanotic episodes*		*During cyanotic episodes*			*Time from onset of apnoea (seconds)*
	*Arterial oxygen saturation** (%)	PaO_2 (*kPa*)	PaO_2 (*kPa*)	*pH*	$PaCO_2$ (*kPa*)	
2†	Not measured	14·0	2·1	7·39	5·1	20
5†	Not measured	12·7	3·0	7·37	5·1	14
8	94	Not measured	2·7	7·43	5·0	18
9	98	Not measured	4·2	7·30	5·1	10
18	98	Not measured	2·8	7·37	4·6	25
36	100	Not measured	3·9	7·39	5·2	15
50	98	Not measured	3·8	7·38	4·5	15
51	99	Not measured	2·9	7·37	5·1	20

*From pulse oximeter (Nellcor N200); †from Southall *et al.*[1]

18 in the sixth, seven in the 12th month, and 24 between 1 and 6 years of age).

Nine healthy, adult volunteers (age 21 to 46 years) underwent tape recordings of breathing movements, oral airflow, and oxygen saturation using the equipment described above, and were asked to breathe out maximally at the end of a normal tidal breath then to hold their breath for as long as possible. The durations of apnoea and the maximum falls in oxygen saturation were documented. In addition, two of the adults underwent krypton-81m infusion scans during which they performed end expiratory breath holding.

TRIALS OF TREATMENT

As cyanotic episodes were precipitated by behaviour associated with stimulation of the sympathetic nervous system and were accompanied by increases in pulmonary artery pressure (see below), tetrabenazine (a centrally acting α-adrenergic antagonist) in doses of 1·0 mg/kg/day in three to four divided doses was given to 15 patients with fully informed parental consent. This therapeutic trial was uncontrolled. Continuous additional inspired oxygen (delivered at 1–2 l/minute using a cannula placed on the upper lip with a fractional inspiratory oxygen (FiO_2) of 35–40%) was given to 10 patients. A combination of tetrabenazine and additional inspired oxygen was given to cases 8 and 22.

Results

FINDINGS DURING CYANOTIC EPISODES

From direct observations by parents, nursing, and medical staff the development of central cyanosis was rapid (within 5–10 seconds of the onset of the breath holding). After 25–30 seconds of progressively severe cyanosis there was a loss of consciousness with opisthotonus or a tonic convulsion, or both. Although surface electroencephalograms showed no seizure activity preceding the cyanosis, at between 25 and 30 seconds into the episode large amplitude slow waves (2 Hz) appeared within all leads with a subsequent lowering of voltage.

Values of arterial oxygen pressure (PaO_2) from radial artery cannulas at specified times after the onset of prolonged expiratory apnoea are shown in table 2. Accurate measurements of oxygen saturation on tape recordings during cyanotic episodes was often not possible because of movement artefacts. In those with adequate signals, arterial oxygen saturation values fell below 50% during all cyanotic episodes recorded.

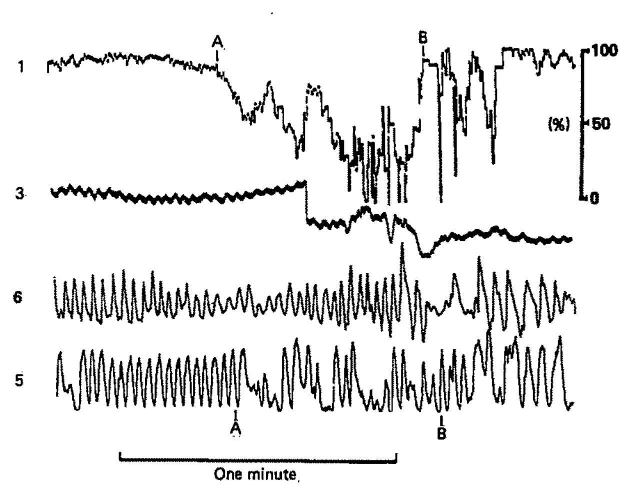
Details of the most common accompanying respiratory pattern, prolonged expiratory apnoea, have been previously reported.[1–3] In around 2% of the cyanotic episodes in which airflow from expired carbon dioxide measurements had been recorded, continued airflow signals were present throughout the hypoxaemic episode (fig 1A and E).

Chest radiographs showed high diaphragms but no atelectasis (results of cases 2 and 10 from reference 1). Krypton-81m inhalation scans showed rapid but incomplete emptying of gas from each lung (37% in 5 seconds and 40% in 11 seconds for case 2, 50% in 32 seconds for patient 10; values corrected for the decay of krypton-81m).[3] Intravenous krypton-81m scans during cyanotic episodes showed an increase in counts over the lung fields coinciding with an increase in mean background body counts (background increase in case 8 from 659 to 1085 (65%), in case 10 from 525 to 856 (63%), in case 22 from 487 to 685 (41%), in case 30 from 303 to 426 (41%), and in case 46 from 613 to 809 (32%)). Mean background body counts during voluntary expiratory apnoea for mean durations of 30 and 50 seconds in the two adult controls changed respectively from 129 to 135 (5%) and 70 to 76 (9%).

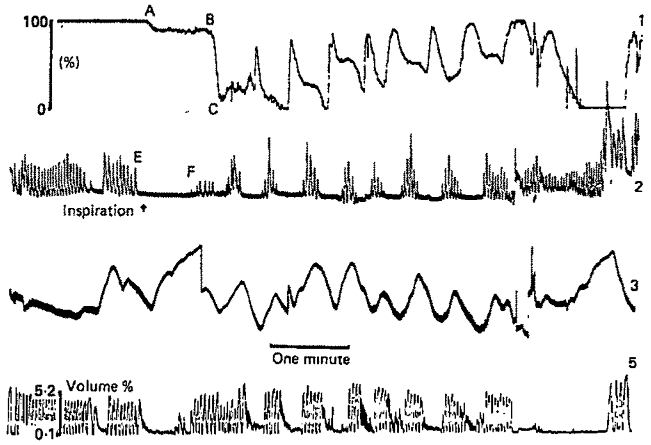
Contrast echocardiography showed no right to left intracardiac passage of air bubbles during cyanotic episodes (results of cases 2 and 5 from reference 1). In addition, no ductus arteriosus was detected in these patients.

The heart rate increased to above 170 bpm at the onset of an episode (fig 2A) but fell to below 80 bpm during the subsequent severe hypoxaemia (fig 2A and B). In around 5% of episodes asystole (≥2·0 seconds) or slow idioventricular escape rhythms occurred at this time. Systemic arterial blood pressure was transiently raised (by 10 to 25 mm Hg) at the onset of the episode in five of nine recorded instances (fig 2A and B). During bradycardia there was an increase in systemic arterial pulse pressure (fig 2A and B) in six of nine recorded instances.

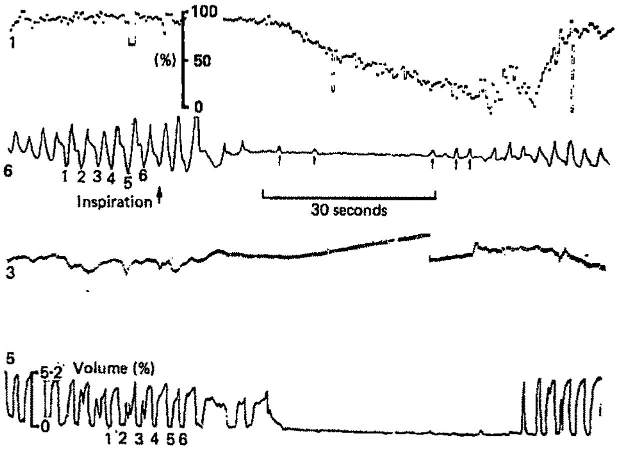
Pulmonary arterial blood pressure was increased during all episodes of hypoxaemia (figs 2A and B) beginning to rise in around a third of instances before the arterial oxygen saturation decreased (as measured using the pulse oximeter in the beat to beat mode (fig 2A). The increase in pulmonary artery pressure included both the diastolic and systolic components with little change in pulse pressure



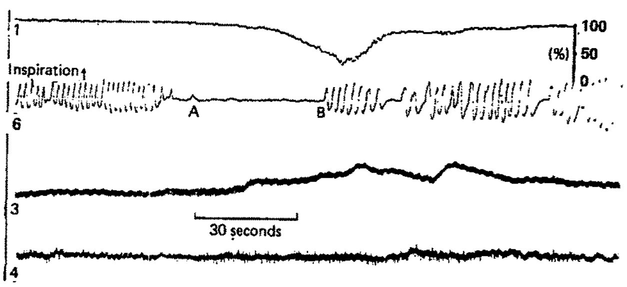
(A) A cyanotic episode that followed a cry and resolved spontaneously without resuscitation. Expiratory airflows and breathing movements continued throughout.



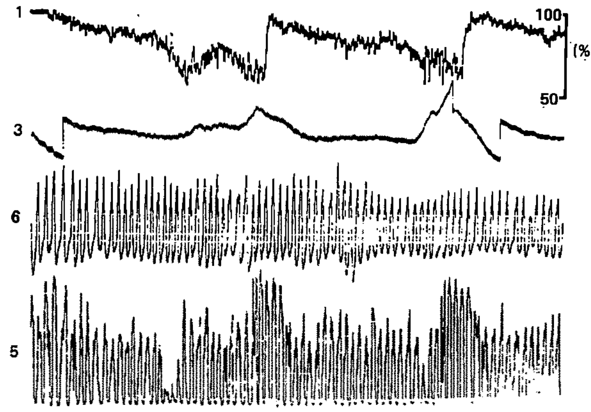
(B) During sleep there was a short apnoeic pause (E–F) accompanied by a small fall (A–B) in arterial oxygen saturation. The latter was followed by a major fall in arterial oxygen saturation (B to C) and subsequently there was an intermittent hypoxaemia accompanied by an episode of periodic apnoea that resolved spontaneously.



(C) Self resolving episode of severe hypoxaemia during sleep. Breathing efforts continued (↑) despite absent airflow. There was no bradycardia.



(D) Self resolving episode of severe hypoxaemia during sleep after a prolonged (37 seconds) apnoeic pause (A to B). There was only a slight fall in heart rate.



(E) Self resolving episodes of hypoxaemia during sleep despite continued breathing movements and continued expiratory airflow. There was no bradycardia.

Figure 1 Comprises five recordings made on case 22 at age 3 months. Signals include (1) beat to beat arterial oxygen saturation from a pulse oximeter (total response time 4 seconds); (2) respiratory inductance plethysmography from a vest placed over the ribcage and abdomen; (3) plethysmographic waveform signals from which arterial oxygen saturation values were computed by the pulse oximeter; (4) electrocardiogram; (5) expired carbon dioxide from a cannula within the external nares (total response time 2·5 seconds); and (6) abdominal wall expansion from a pressure capsule transducer.

until bradycardia developed. Pulmonary artery pressures before hypoxaemia ranged from 22/4 to 30/24 mm Hg. At their maximal values they ranged from 53/40 to 105/65 mm Hg.

Fibreoptic endoscopy during cyanotic episodes showed an initial vocal cord adduction (reported in cases 2, 3, and 7 in reference 1). In nine patients (cases 1–3, 5, 18, 22, 23, 33, and 38), cyanotic episodes continued despite bypass of the upper airway using an endotracheal tube or tracheostomy. Hypoxaemic episodes also occurred in five of these (1, 2, 18, 22, and 23) despite intermittent positive airway pressure ventilation (IPPV).

When attempting to resuscitate patients using bag and facemask ventilation, there was pronounced difficulty in inflating the lungs initially. Even when the upper airway was bypassed

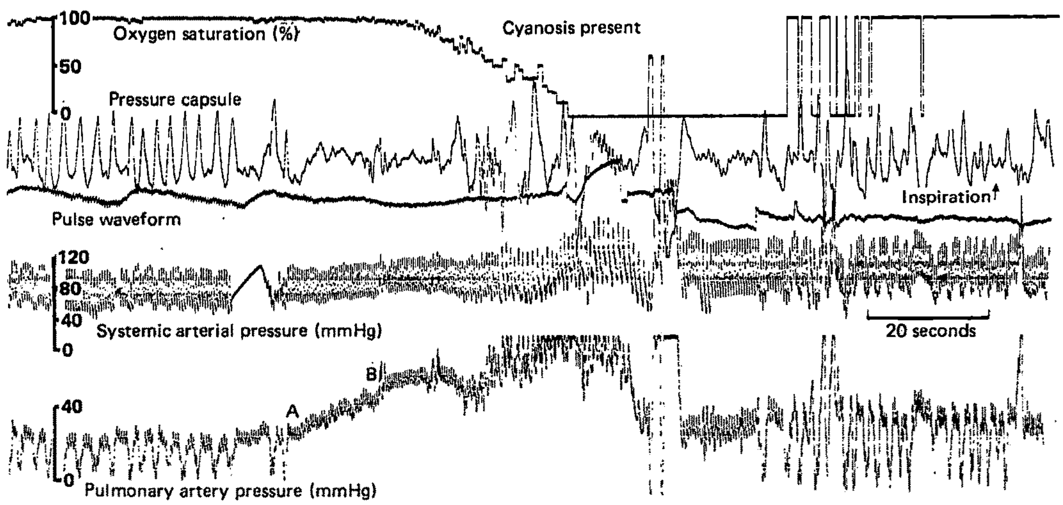


*Figure 2 (A) An episode of severe hypoxaemia in case 18 (who had a tracheostomy). Allowing for a 4 second total response time of the oximeter, pulmonary artery pressure increased (**A** to **B**) before arterial oxygen saturation began to fall. Pulmonary artery pressure continued to rise while hypoxaemia progressed reaching a peak value of 77/49 mm Hg. At this point there was a bradycardia and increase in pulse pressure in both systemic and pulmonary arteries. The loss of systemic arterial pressure at the onset of the episode was probably artefactual.*

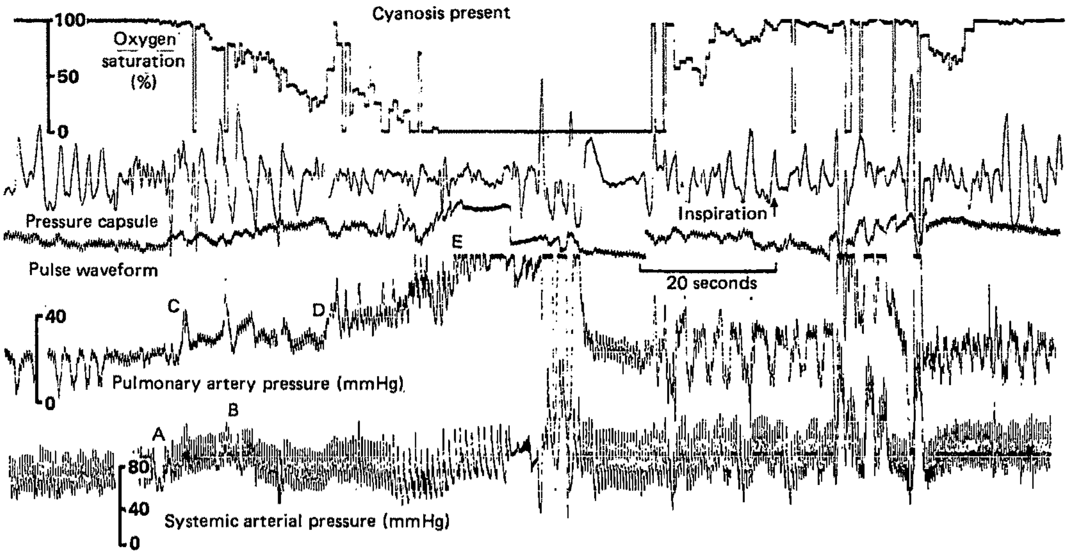


*Figure 2 (B) A further cyanotic episode in case 18. On this occasion the pulmonary artery pressure increased (**C** to **D**) from the beginning of the fall in arterial oxygen saturation. The rate of rise in pulmonary artery pressure increased as hypoxaemia became more severe (**D** to **E**). At the onset of the cyanotic episode there was an increase (**A** to **B**) in systemic blood pressure.*

using a tracheostomy or endotracheal tube, large inflation pressures were required. With recovery, effective inflation pressures rapidly decreased.

In case 21 (who had undergone repair of a tracheo-oesophageal fistula) cyanotic episodes were reproducibly induced by inflating a latex balloon (length 45 mm, diameter 10 mm) within the upper third of the oesophagus. Oesophagoscopy showed a fusiform dilatation above a strictured area at the site of the original repair. Episodes requiring resuscitation and subsequent ventilation continued, however, despite dilatation of this stricture. He subsequently underwent an aortopexy and Nissen fundoplication, after which episodes were reduced from every two or three days to every one or two weeks. Case 3, who had undergone repair of a tracheo-oesophageal fistula, underwent tracheostomy because acute airway obstruction caused by tracheomalacia was considered to be the cause of his hypoxaemic episodes. About nine out of 10 of his episodes occurred after crying rather than with swallowing. Even with a special tracheostomy tube inserted to lie 1 cm above the carina, there was no reduction in the frequency or severity of his episodes.

In case 10, 18% inspired oxygen given by a headbox during sleep produced cyanosis with oxygen saturation of less than 50%, prolonged expiratory apnoea, and arousal. (The effects of breathing 15% oxygen when awake in this subject have been reported by Southall *et al.*[1])

End expiratory breath holding manoeuvres in cases 3 and 32 produced the following maximum apnoeic pauses and falls in arterial oxygen saturation: 19 and 21 seconds with a saturation of 95 and 93% (case 32), 9 and 13 seconds with a saturation of 98 and 95% (case 3).

The duration of apnoea (seconds) and in brackets the lowest arterial oxygen saturation values (%) attained by nine adult controls during forced end expiratory breath holding were: 31 (87), 15 (84), 25 (87), 24 (98), 19 (94), 32 (79), 27 (92), 18 (96), and 27 (88).

Findings at the end of the cyanotic episodes have been previously described.[1–3]

FINDINGS BETWEEN CYANOTIC EPISODES

Apart from patients with brainstem lesions, overnight tape recordings failed to show any abnormalities.

Tape recordings on cases 8, 22, 24, and 25, all of whom had brainstem abnormalities, showed self correcting episodes of hypoxaemia (<60% arterial oxygen saturation) occurring up to 30 times/hour and accompanied by one of three patterns: (i) continued breathing movements but with absent inspiratory airflow (fig 1C); (ii) prolonged absence (>20 seconds) of breathing efforts (fig 1D); and (iii) continued breathing movements and continued airflow (fig 1E). None of the overnight tape recordings of the control subjects showed prolonged apnoeic pauses (>20 seconds), hypoxaemia (arterial oxygen saturation <60%), or expiratory braking with hypoxaemia.

UNCONTROLLED TRIALS OF TREATMENT

From an examination of parental diaries, ward charts, and continuous tape recordings of arterial oxygen saturation and breathing activity, the average number of cyanotic episodes/week accompanied by prolonged (≥20 seconds) expiratory apnoea was documented in each patient before and after receiving tetrabenazine and additional inspired oxygen, respectively.

The median in 15 patients before receiving tetrabenazine was 14 (range 3 to 60) and after receiving tetrabenazine was 0 (range 0 to 25) episodes/week. All 15 patients (100%) showed an improvement, a finding that is significantly different from the 50% expected by chance (one sided binomial test, $p=0\cdot00003$).

The median before additional inspired oxygen in 10 patients was 21 (range 3 to 175) and after oxygen was 4 (range 0 to 35) episodes/week. Seven out of 10 showed an improvement, a finding that is significantly different from the 50% expected by chance (one sided binominal test, $p=0\cdot008$). Cases 8 and 22 were receiving additional inspired oxygen when tetrabenazine was added.

The recent addition of a small dose of clonidine to the tetrabenazine appeared more effective than tetrabenazine alone.

OUTCOME

Four patients died suddenly during or directly as a consequence of a cyanotic episode.

Case 7

This girl had undergone repair of a tracheo-oesophageal fistula and died aged 2·9 years while swallowing solid food. This seemed to stick in her oesophagus, she developed severe cyanosis, and died before reaching hospital. Similar cyanotic episodes had occurred since the age of 3 months.[7] At necropsy there was fusiform dilatation of the upper third of the oesophagus in which was lodged a piece of solid food. No food was found in the airway. Immediately below the dilatation there was an area in which the muscle of the oesophagus was interspersed with some fibrotic tissue and a proliferation of nerve fibres.

Case 18

This girl died aged 3·6 years during a cyanotic episode that did not respond to positive airway pressure ventilation through her tracheostomy that was applied within 20 seconds of the onset of the cyanosis and accompanied by definite ventilation throughout the entire attempt at resuscitation. At necropsy there was a small area of bronchopneumonia, and mucus in the trachea and bronchi.

Case 23

This baby boy died aged 11 months after a typical cyanotic breath holding episode induced by a cry, which produced irreversible brain damage and was fatal within 48 hours. He had been extensively investigated for such episodes and had a tracheostomy in place to aid resuscitation. Episodes had occurred before death despite continued inspiratory and expiratory airflow and IPPV through a tracheostomy tube. There was progressive neurodevelopmental impairment and sequential computed tomograms showed evidence of progressive cerebral atrophy, probably the result of his episodes of severe cerebral hypoxaemia. At necropsy there was enlargement of the trachea below the tracheostomy, mucosal inflammation of the tracheobronchial tree, and areas of bronchopneumonia.

Case 27

This girl died aged 1·5 years during a typical cyanotic breath holding episode after a cry. She had a cleft palate and had suffered a total of seven similar episodes, which had begun only four weeks before her death.[7] At necropsy there was pulmonary oedema but no structural abnormality of the airway.

Four additional boys (cases 35, 38, 41, and 48) each giving a history of typical cyanotic breath holding episodes died aged 2, 35, 5, and 6 months, respectively. These deaths were all sudden and unexpected; all four were found dead when their parents awoke in the morning. In all but case 38 there was no adequate explanation for the death at necropsy.

A necropsy on case 35 showed milk curds in the larynx, intrathoracic petechial haemorrhages, and pulmonary oedema. The cause of death was given as 'sudden infant death syndrome (milk aspiration)'.

Case 38 had had severe cyanotic episodes since he was 4 months of age. On the night before death, at the age of 2·9 years, he had had a severe episode of cyanosis accompanied as usual by profuse sweating. The following morning he was found dead and at necropsy a glioma was found in the medulla.[8]

A necropsy on case 41 showed congested airways and haemorrhagic pulmonary oedema. The cause of death was given as acute bronchopneumonia (probably viral).

A necropsy on case 48 showed numerous petechial haemorrhages on the visceral pleura, epicardium, and intrathoracic thymus. Pulmonary oedema was also present. The cause of death was given as sudden infant death syndrome.

Cases 2, 8, 10, 17, 18, 23, and 34 had neurodevelopmental impairment that seemed to progress during times at which episodes were most frequent and severe.

Discussion

All our patients had cyanotic episodes associated with recurrent loss of consciousness. The most common trigger was a sudden, naturally occurring stimulus from pain, fear, or anger. These episodes are therefore equivalent to cyanotic breath holding with our patients at the severe end of the range of this common paediatric problem.[5] Although our patients presented early in life, the age at onset and the incidence of a positive family history is similar to that described by Lombroso and Lerman.[5] The 28 of our patients who underwent physiological recordings, however, had severe and frequent episodes that were considered to be life threatening. Investigations to gain a better understanding of their pathophysiology, and uncontrolled trials of treatment, were considered essential. Even in those patients with the most frequent and severe episodes, the relatively unpredictable timing, the need for resuscitation, and ethical concerns limited the information that could be collected.

Characteristically the onset of severe cyanosis was rapid (within 5–10 seconds), with loss of consciousness at around 25–30 seconds. Although prolonged expiratory apnoea and laryngeal adduction were features of the cyanotic episodes, severe hypoxaemia sometimes occurred despite continued airflow (figs 1A and 1E), endotracheal intubation, and IPPV. These features exclude primary upper airway obstruction as the cause of hypoxaemia.

Prolonged expiratory apnoea will contribute to hypoxaemia by reducing the content of oxygen available to perfused alveoli.[1] Accepting the rapid total circulatory times of infants and young children at rest (5–9 seconds),[9] is this mechanism alone sufficient to cause such severe hypoxaemia? Only a mild degree of hypoxaemia was documented after end expiratory breath holding in two of our patients, in our adult controls, and by Findley *et al.*[10] There is, however, limited value in comparing adults with infants because of differences in their closing volumes. Nevertheless the development of severe hypoxaemia, despite IPPV or continued spontaneous ventilation, suggests that apnoea contributed to, but was not the main cause of, the hypoxaemia. Moreover, during imposed airway obstruction,[11] hypoxaemia sufficient to produce electroencephalographic changes of cerebral hypoxia occurred after a delay of 60–70 seconds compared with only 25–30 seconds in our patients.

The rapid onset and progression of severe hypoxaemia in the presence of continued ventilation, together with the appearance of infused krypton outside the lung fields, suggested a right to left shunt. As contrast echocardiography failed to show an intracardiac pathway, the shunt must have been intrapulmonary.

Krypton infusion scans do not allow the shunt to be quantified. During apnoea, background counts may increase due to raised concentrations of krypton in pulmonary veins. Adult controls, however, did not show increased background counts during prolonged expiratory apnoea. Future studies with technetium labelled microspheres may provide more information on the size of the shunt.

Intrapulmonary shunting may arise from the continued or increased perfusion of unventilated alveoli (small airway obstruction or atelectasis) or from the diversion of a proportion of pulmonary arteriolar blood into pulmonary venules without contact with a gas exchanging surface. In previous reports we suggested that a shunt might have resulted from atelectasis caused by a primary defect in lung surfactant.[2] Our data continue to show reduced lung compliance during the latter part of each episode.[1–3] The results of radiographic and krypton imaging during the cyanosis, however, together with the increase in pulmonary artery pressure that sometimes preceded the fall in arterial oxygen saturation (fig 2A) suggests that although the shunt may have resulted from atelectasis or small airway closure it was more likely to have arisen from a primary disturbance in the distribution of pulmonary blood flow. An increase in pulmonary vascular resistance and therefore in pulmonary artery pressure after the hypoxaemia would be expected. A rise in pulmonary artery pressure before the hypoxaemia, however, suggests that an intrapulmonary shunt is a consequence as well as a cause of the increased pulmonary artery pressure. Whether the latter is the result of increased cardiac output or increased pulmonary vascular resistance cannot be answered from our data. Lung perfusion scans in newborn lambs,[12] and in adult humans who developed pulmonary oedema at high altitude,[13] have shown that the pulmonary vasoconstriction that results from airway hypoxia is not uniform; the accompanying increase in pulmonary artery pressure redistributes flow and produces a shunt that is accompanied by an increased filtration of fluid across the alveolar-capillary junction. As to the site of the shunt, bronchopulmonary and other anatomical arteriovenous anastomoses have been described in the human lung,[14] and recently Wilkinson and Fagan (Intrapulmonary arteriovenous shunting in cot deaths. Presented at the 35th meeting of the Paediatric Pathology Society, 1989) using a 2% gelatin solution and microspheres (64 μ in diameter) injected into the pulmonary artery showed that a proportion of infants who died suddenly had intrapulmonary arteriovenous pathways by-passing the pulmonary capillary bed. Moreover, young infants have an increased tendency to venous admixture, which is thought to be related to a paucity of alveoli compared with lung capillaries.[15] Increased perfusion of this immature gas exchanging surface may also lead to a shunt.

Modifications to airway PO_2 have provided additional support for the role of pulmonary vasoconstriction in the genesis of the shunt. Thus an increased FiO_2 reduced the frequency and severity of episodes and, in one patient, a reduced FiO_2 precipitated cyanotic episodes. Moreover, cyanotic episodes were sometimes precipitated by short normal apnoeic pauses, (fig 1B) a natural mechanism for producing transient airway hypoxia. Changes in pulmonary vasomotor tone in response to airway PO_2 levels, may be mediated through the pulmonary neuroendocrine cell system, airway cells that may influence ventilation to perfusion matching.[16] In the fetus, which has a low lung liquid PO_2, these cells may help to maintain pulmonary vasoconstriction.[17] Disturbances in the number, size, or innervation of these cells, perhaps following chronic prenatal or postnatal airway hypoxia, may predispose to intrapulmonary shunting.[18]

The observation that stimuli known to induce sympathetic activity precipitate cyanotic episodes, together with the uncontrolled results of treatment with tetrabenazine, latterly in combination with clonidine, suggest that pulmonary vasoconstriction, mediated by adrenergic pathways, is a primary component in the genesis of the shunt. As prolonged expiratory apnoea and hypoxaemia continued to occur in response to crying despite an FiO_2 of 1·0,[1] adrenergic discharge may over-ride the protection provided by a high airway PO_2.

A mild degree of cyanosis on crying is common in most young children, suggesting that a degree of intrapulmonary shunting is possible in otherwise healthy subjects. In our patients with severe hypoxaemic episodes it is possible that there is a functional or structural potential for increased shunting in the pulmonary vascular bed, that there is an excessive adrenergic discharge, or that there is an enhanced response to a fall in airway PO_2, or all three.

Five patients had brainstem abnormalities and similar cyanotic episodes have been previously reported in patients with meningomyelocoeles,[19] and with brainstem tumours.[8] Brainstem defects may produce these cyanotic episodes by a number of different mechanisms including disturbances to the respiratory generators, to the centres controlling pulmonary vasomotor tone, and to the processing of reflexes arising in the pulmonary vascular bed or lung. Long has shown that stimulation of the brainstem vasomotor centre in piglets can induce pulmonary vasoconstriction.[20]

The cyanotic episodes that follow tracheooesophageal fistula repair,[21] or occur in patients with vascular rings,[22] may also result from mechanical stimulation of the trachea or oesophagus. In one patient, hypoxaemia followed balloon inflation within the oesophagus, supporting previous observations that absent inspiratory efforts and not obstructed inspiratory efforts were present during cyanotic episodes in patients with similar anomalies.[21 22] Fearon and Shortreed also induced absent inspiratory efforts under light general anaesthetic when a bronchoscope was passed through the compressed area of trachea, a response that was not seen with deep anaesthesia.[22] In addition, abnormal nerve fibres around the oesophagus were seen at necropsy in case 7, who died during a cyanotic episode induced by a bolus of food that lodged within the oesophagus.[7] Afferent impulses from around the trachea and oesophagus may therefore also precipitate intrapulmonary shunting, possibly through reflexes involving sympathetic efferent activity from the brainstem.[20]

The mechanisms responsible for the prolonged expiratory apnoea that accompanied and contributed to the hypoxaemia remains uncertain. A degree of breath holding normally follows emotional stimuli in many infants and young children,[23] but in our patients this response is prolonged for reasons which remain at present unknown. Evidence that prolonged apnoea may occur with noradrenergic stimulation of the brainstem may be relevant to this latter observation.[24] Pulmonary C fibre receptors[25] may also be stimulated by a pulmonary transudate in the alveolar-capillary junction resulting from pulmonary vasoconstriction.[12]

The first breaths that occur as the cyanotic episode ends show expiratory braking, a variable dynamic lung compliance, a continued increase in lung volumes following the end of each inspiratory effort, and variability of ventilation on the krypton inhalation scans.[1–3] Changes in compliance may result from induced defects in the lung surfactant system,[2] from pulmonary oedema, and from areas of decreased pulmonary capillary filling leading to loss of erectile support.[26]

As eight of our 51 patients (16%) died suddenly and unexpectedly (four during a cyanotic episode) the mechanisms outlined above are a potential pathway to sudden death in infancy and early childhood. The compatibility of this hypothesis with some of the known epidemiological, physiological, and pathological features of sudden unexplained infant death syndrome (SIDS) has been considered.[27] Additional evidence is given by the age of onset of these cyanotic episodes (similar to SIDS) and our observation that disturbances in daily routine, reported in association with SIDS,[28] were accompanied by an increased number of cyanotic episodes in our patients. The timescale of SIDS (sparing the first 4 weeks, peaking from 6 weeks to 4 months) may represent a vulnerable period related to postnatal remodelling and control of the pulmonary vascular bed.[29] The higher incidence of SIDS after a suboptimal prenatal environment might be related to the impact of fetal lung fluid hypoxia on the development of the pulmonary vasculature or neuroendocrine systems.[30–32] Kinney and Filiano, using neurochemical techniques, have shown that there are disturbances in the region of the brainstem vasomotor centres in SIDS victims.[33] The presence of pulmonary oedema in almost all babies who die of SIDS may also be the result of intrapulmonary shunting.[34] The presence of petechial haemorrhages in babies who die of SIDS has also been produced experimentally by hypoxaemia and by noradrenaline infusion.[35]

In conclusion, the cyanotic episodes described here were accompanied by severe arterial and cerebral hypoxaemia. They have been previously described as cyanotic breath holding attacks, and are induced both by behavioural activity and in response to afferent impulses arising from within and around the respiratory tract. The resulting intrapulmonary shunt and prolonged expiratory apnoea are probably mediated through the brain stem vasomotor and respiratory control centres. As these episodes may cause sudden death and neurological impairment, we suggest that they should be subject to further research and to trials of treatment, particularly when they occur in young infants or are accompanied by recurrent loss of consciousness.

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Carpal tunnel syndrome in the mucopolysaccharidoses and related disorders

J E Wraith, S M Alani

Abstract

Eighteen patients with various mucopolysaccharidoses or mucolipidosis III were studied electrophysiologically to determine the presence or absence of carpal tunnel syndrome. In 17 patients this was clearly demonstrated, the only exception being a boy with mucopolysaccharidosis II, age 6 months at testing. All patients had a remarkable lack of symptoms.

Carpal tunnel syndrome is a very common complication of the mucopolysaccharidoses and mucolipidosis III and should be actively looked for in affected patients. Early diagnosis and treatment offer the best chance of a good response to surgery.

The mucopolysaccharidoses are a group of inherited disorders caused by a deficiency of specific lysosomal enzymes. The enzyme deficiency causes interference with cellular function because of excessive accumulation within the cells of partially degraded glycosaminoglycans, which are also excreted to excess in the urine of affected patients.[1] Mucolipidosis III is a related disorder caused by an inherited deficiency of the enzyme necessary for complete post-translational processing of lysosomal hydrolases. The clinical features produced by this enzyme deficiency mimic those of some of the mucopolysaccharidoses.[2, 3]

Carpal tunnel syndrome is the commonest of the entrapment neuropathies, but it is rare in childhood. It is known to occur in association with the mucopolysaccharidoses or mucolipidosis III, as well as other systemic disorders.[4–10]

A number of the patients with one of the mucopolysaccharidoses or mucolipidosis III are mildly affected by their disease and of normal intelligence, and these patients may have a good prognosis in terms of life expectancy. The loss of thumb function due to carpal tunnel syndrome can be a severe handicap especially as the skeletal dysplasia commonly present can also lead to restricted hand mobility.

We present a study on the incidence and age of onset of carpal tunnel syndrome in a group of 18 patients with one of the mucopolysaccharidoses or mucolipidosis III attending the Manchester mucopolysaccharidoses clinic.

Patients and methods

Eighteen patients with various types of mucopolysaccharidosis or mucolipidosis III were studied. The age at testing and results of electrophysiological studies are shown in the table.

All patients had a standard neurological examination. Sensation over the territory of the median nerve was assessed by the patients' ability to appreciate pinprick and being touched lightly with cotton wool in those who were old enough to cooperate with sensory testing.

Nerve conduction studies were performed using a Medelec MS91 electromyelography system. Median and ulnar sensory action potentials were recorded with surface electrodes placed over the median or ulnar nerves at the

Electrophysiological results

Patient No	Age (years)	Sex	Diagnosis*	Distal motor latency (ms)			Sensory action potential (ms)		
				Right	Left	Mean (SD) normal†	Right	Left	Mean (SD) normal†
1	1·2	M	MPS I H	4·6	4·6	2·00 (0·23)	2·6	3·0	1·20 (0·1)
2‡	9	M	MPS I H	3·4	3·1	2·50 (0·20)	Absent	Absent	1·06 (0·1)
3§	9	M	MPS I H	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
4	7	F	MPS I S	5·0	2·2	2·50 (0·20)	Absent	1·2	1·20 (0·1)
5	8	M	MPS I S	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
6	10	F	MPS I S	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
7	9	F	MPS I S	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
8	16	M	MPS I S	4·8	10	2·50 (0·20)	Absent	3·8	1·06 (0·1)
9	0·5	M	MPS II	2·2	2·0	2·12 (0·34)	1·4	1·2	1·20 (0·2)
10	1·7	M	MPS II	6·8	6·0	2·00 (0·23)	2·2	3·1	1·20 (0·1)
11	2·5	M	MPS II	Absent	Absent	2·17 (0·14)	Absent	Absent	1·10 (0·1)
12	3	M	MPS II	4·6	5·4	2·17 (0·14)	3·2	2·4	1·10 (0·1)
13	25	M	MPS II	Absent	Absent	3·20 (0·40)	Absent	Absent	0·90 (0·1)
14	16	F	MPS VI	8·5	6·6	2·50 (0·20)	Absent	4·6	1·06 (0·1)
15	8	F	ML III	2·6	2·9	2·50 (0·20)	Absent	Absent	1·06 (0·1)
16	9	F	ML III	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
17	10	M	ML III	Absent	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)
18	14	F	ML III	3·8	Absent	2·50 (0·20)	Absent	Absent	1·06 (0·1)

*MPS I H: mucopolysaccharidosis type I, Hurler's syndrome; MPS I S: mucopolysaccharidosis type I, Scheie's syndrome; MPS II: mucopolysaccharidosis type II, Hunter's syndrome; MPS VI: mucopolysaccharidosis type VI, Maroteaux-Lamy syndrome; ML III: mucolipidosis type III, pseudo-Hurler polydystrophy.
†See Cruz Martinez *et al.*[11]
Bone marrow transplant ‡ at age 14 months; § at age 2·3 years (both at Westminster Children's Hospital).

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wrist separately after application of supramaximal stimuli of 0·1 ms duration at 1/second to the index and little finger, respectively, using ring electrodes with the cathode proximal. Ten potentials were averaged and latency to onset, peak to peak amplitude, and sensory nerve conduction velocity were measured.

The median motor response was recorded over the abductor pollicis brevis with surface electrodes after supramaximal stimulation of the median nerve at the wrist and elbow. The latency to onset, the amplitude of the negative component of the motor response at each site, and the motor conduction velocity were measured.

The median sensory response was considered abnormal if the potential was absent, smaller, or its latency 1 ms or more longer than that of the ipsilateral ulnar sensory potential. The median motor velocity was considered abnormal if absent or its latency was outside the normal range for age.[11]

Results

No patient or parent reported symptoms suggestive of carpal tunnel syndrome, such as parasthesiae or nocturnal pain.

All patients with the exception of those under the age of 2 years at testing (patients 1, 9, and 10) had clear evidence of wasting of the thenar muscles as well as the typical 'claw hand' deformity seen in the mucopolysaccharidoses and related disorders.

In those patients old enough to cooperate with sensory testing, impaired sensation to pinprick and cotton wool was present despite the absence of parasthesiae. Tinel's sign was persistently negative.

The results of electrophysiological studies are shown in the table. Only patient 9, aged 6 months at testing, had normal median nerve conduction. His older sibling (patient 10), had clear neurophysiological evidence of carpal tunnel syndrome at 1·7 years and it will be interesting to document the onset in patient 9. Patient 4 was also slightly unusual in that her carpal tunnel syndrome was unilateral, affecting only the right hand (she is right handed). There was no clinical or neurophysiological evidence of other entrapment syndromes in any of the patients.

Decompression of the median nerve was performed by a longitudinal incision at the wrist in all patients except patients 1 and 11. At operation the flexor retinaculum appeared swollen in some patients; the nerve itself looked normal. Biopsy specimens of the flexor retinaculum were examined under the electron microscope. In all cases examined prominent lysosomal distension was seen within the fibroblast cell. Patients who have been operated upon have been followed up by regular electrophysiological testing. So far only patients 10 and 14 show improvement from their preoperative electrophysiological tests, both six months after operation. In contrast most patients and parents have reported symptomatic improvement in hand function. Detailed follow up studies of hand function in these patients are currently in progress.

Discussion

Carpal tunnel syndrome appears to be a common complication of the mucopolysaccharidoses and mucolipidosis III and is probably due to a combination of excessive lysosomal storage in the connective tissue of the flexor retinaculum as well as a deformed anatomy because of the underlying bone dysplasia. It occurs early in the course of the disorders and the long standing nature of the compression may explain the lack of typical symptoms in all the patients studied. This would also imply a poor response to surgical decompression and indicate the need to be aware of this possible complication in all patients with one of the mucopolysaccharidoses or mucolipidosis III. Those patients who have a mild variant need urgent diagnosis and treatment as the other complications of the disorders usually mean that in affected adults a clerical occupation, often requiring manual dexterity (for example, word processing) is the most suitable form of employment. In patients with severe variants of the mucopolysaccharidoses it is debatable whether or not the treatment of carpal tunnel syndrome justifies the risk of operation to release the nerve in a child whose life expectancy is very limited.

It is interesting to speculate why the bone marrow transplantation failed to prevent or reverse the carpal tunnel syndrome in patients 2 and 3. It is likely that it was already present at transplant and the relatively avascular nature of the flexor retinaculum may make it difficult for donor enzyme to penetrate this dense connective tissue. In patients thought suitable candidates for bone marrow transplantation carpal tunnel syndrome should be sought and treated if present.

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Natural and modified history of complete atrioventricular septal defect—a 17 year study

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Abstract

We reviewed 103 cases of isolated complete atrioventricular septal defect. These cases represented 4·4% of the cases of congenital heart disease diagnosed in our hospital by catheterisation and angiography during 1971–88. Most children (n=76) had Down's syndrome. Banding of the pulmonary artery was peformed in seven cases and complete repair in 67 cases. In the period 1971–82 the complete correction was performed at a mean age of 23 months with a surgical mortality of 88·8%. In the period 1983–8 the mean age at complete correction was 13 months, the mortality 43·2%, and the five year actuarial survival was 46·8%. The 22 patients that survived after complete correction were in functional classes I and II of the New York Heart Association classification. After a mean follow up of 10 years only eight (36%) of the 22 who were followed up and treated medically survived; all had developed pulmonary vascular obstructive disease and were in functional classes III or IV. Our findings stress the importance of early complete surgical repair.

Although there has been discussion on the natural history of complete atrioventricular septal defect, the general view is that all untreated cases develop obstructive pulmonary vascular disease.[1 2] On the basis of necropsy findings Berger *et al* concluded that the survival at 6 months, 2 years, and 5 years of age is about 50, 15, and 4% respectively.[3] Nevertheless, these data may not reflect the true natural history of this malformation, as many cases develop Eisenmenger's syndrome, and may survive for many years, although with a very limited quality of life.[4 5]

Complete surgical correction offers the only present possibility of long term survival, but it is technically difficult. Since Newfeld *et al* showed that the pulmonary vascular changes may progress to fibrosis of the intima, grade III within six months, and to grade IV within a year,[6] it appears that the surgical correction should be attempted early. In fact, in all series reported there was a high proportion of children not eligible for surgical correction because of pulmonary vascular obstructive disease.[7–9] The vascular disease may develop faster in children with Down's syndrome, and they constitute most of the patients with this malformation.[10 11]

We reviewed the 103 cases of isolated complete atrioventricular septal defect diagnosed and treated at the Children's Hospital 'La Fe', Valencia, since 1971 to determine more about the development and prognosis of this malformation.

Patients and methods

The complete atrioventricular septal defect is characterised by a large atrioventricular septal defect, by a common atrioventricular valve that originates from both atria, and with deficiency of the ventricular septum.[12] Using angiohaemodynamic methods, 103 children had a complete atrioventricular defect diagnosed at this hospital from January 1971 to January 1988; these children had no other cardiac anomalies. These patients accounted for 4·4% of the 2322 children who had congenital heart defects diagnosed by cardiac catheterisation and angiography in this hospital during the period of the study. Patients with partial atrioventricular septal defects ('ostium primum') or with associated complex anomalies such as tetralogy of Fallot, left ventricular outflow obstruction, or double outlet right ventricle were excluded. Cases with associated patent ductus arteriosus and cases with the 'intermediate form' of atrioventricular septal defect, with fusion of the anterior and posterior bridging leaflets atop the ventricular septum, but with a functionally large ventricular septal defect, were included.[12] Of the 103 cases studied, 60 had the Rastelli type A, two type B, 30 type C, and 11 the 'intermediate form'.[12] Seventy six of the 103 cases (74%) were patients with Down's syndrome diagnosed cytogenetically. Seventy three of the 103 children were treated surgically (71%). The mean follow up period was 10 years.

We used the functional classification criteria of the New York Heart Association (NYHA): class I, no cardiac symptoms with ordinary activity; class II, no symptoms at rest but some limiting symptoms with ordinary activity; class III, appreciable limitation of physical activity; and class IV, cardiac symptoms at rest. The actuarial survival curves were constructed according to the modification of Anderson *et al*[13] of the method of Kaplan and Meier.[14]

Results

OVERALL SURVIVAL

At the end of the follow up period, 62 patients (60%) had died, 33 (32%) survived, and eight were lost to the study.

NATURAL HISTORY

Of the 30 children treated non-surgically, in eight cases of Down's syndrome the parents refused the surgical repair, the patients failed to keep subsequent appointments, and were lost to the study at a mean age of 3·5 years; their fate is unknown.

Fourteen children died (64% of the non-surgical group who were followed up): 13 within the first year (mean five months) from congestive heart failure or respiratory complications, and one at 6 years of age with Eisenmenger's syndrome. The remaining eight cases were alive at the last evaluation in 1989, had Eisenmenger's syndrome with functional class grades III or IV of the NYHA classification, and now are considered inoperable. Their clinical deterioration occurred between 1 and 3 years of life.

MODIFIED HISTORY

Of the seven children treated with banding of the pulmonary artery, three died in the immediate postoperative period, one developed obstructive pulmonary vascular disease and is not eligible for complete correction, one died during complete correction performed later, and two are awaiting complete correction.

Complete correction was performed in 67 children at a mean age of 20 months. Of these, 45 died (43 perioperatively and two late after operation). The 22 survivors of the complete repair have been followed up for a mean of 6·5 years postoperatively. The functional results are good, despite the existence of mild to moderate mitral regurgitation. In the last evaluation in 1989 their clinical state in all cases was within classes I or II of the NYHA classification.

Although the overall surgical mortality was high (65·7%; 67·2% for the complete correction) this was due in part to 88·8% mortality in the period 1971–82; in that period 36 (65%) of 55 cases diagnosed were operated on at a mean age of 23 months. Since then 37 (77%) of 48 children diagnosed have been operated on at a mean age of 13 months, with a mortality of 43·2%.

ACTUARIAL SURVIVAL CURVES

In the curve for the 103 children studied (fig 1), 23 of the children (37% of the deaths) died within the first year, only 41·9% survived to the end of the third year, and, at the end of the sixth year the survival was 28·5% and the curve approached a plateau.

Figure 2 compares the survival of the 55 children diagnosed in the period 1971–82 with that of the 48 patients diagnosed in the period 1983–8. For the former period the curve flattens after four years and only 16·4% of the patients survived. For the latter, 53·3% survived six years and 32·0% after six years. The difference in survival is significant for all points from one to five years.

The curve for the 36 children operated in the period 1971–82 (fig 3) shows that only 11·1% survived after four years. For the 37 children operated in the period 1983–8 the shape of the curve in the first years is rather similar to that for the period 1971–82, but the curve flattens off much earlier than for the former group, and the survival was about 50% at two years, and 46·8% at the plateau. The differences in survival between the two groups are significant for the points between one and five years.

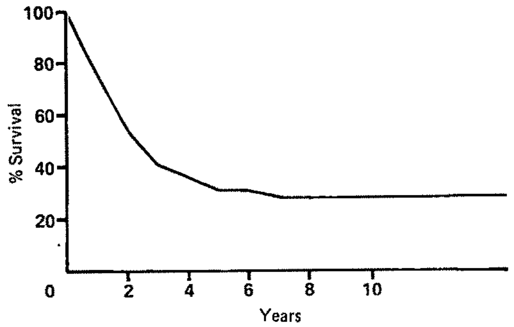

Figure 1 Combined natural and modified actuarial survival of 103 children with complete atrioventricular canal diagnosed in the period 1971–88.

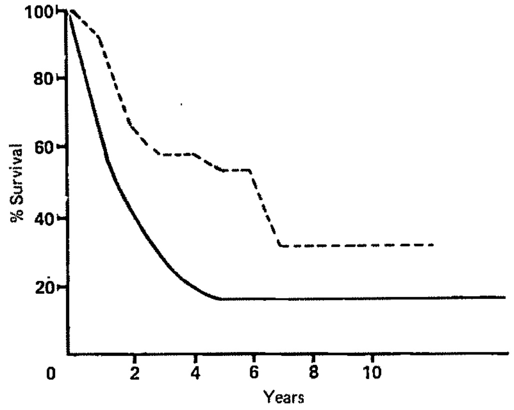

Figure 2 Combined natural and modified actuarial survival of 55 children with complete atrioventricular canal diagnosed in the period 1971–82 (continuous line), and 48 children diagnosed in the period 1983–8 (dotted line).

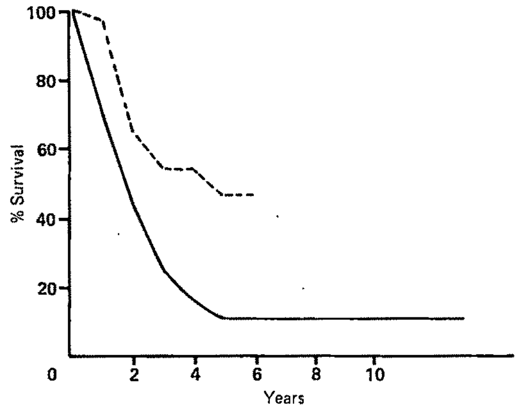

Figure 3 Actuarial survival of 36 children with complete atrioventricular canal operated in the period 1971–82 (continuous line) and 37 children operated in the period 1983–8 (dotted line).

Discussion

The relative incidence of this cardiac malformation in our series (4·4% of the congenital heart defects diagnosed by angiohaemodynamic study) is higher than that reported in other series that include congenital heart defects diagnosed by non-invasive methods.[15 16] This difference probably reflects the bias of the diagnostic method used here, which favours the inclusion of patients with serious defects.

Despite the fact that 35% of the patients follow up and treated medically have survived, they are in functional class III or IV of the NYHA classification, have poor quality of life, and an unfavourable outlook, thus confirming that non-surgical management of this malformation yields very poor results.

The palliative operation adds risk to the complete correction to be performed later, does not always prevent pulmonary vascular obstructive disease (as illustrated in one of our cases), and was associated, in our study, with a high surgical mortality. Our policy at present is to use the palliative procedure only in cases with left ventricular hypoplasia.[17 18]

Although the overall surgical mortality of the complete repair was very high, the results for the period 1983–8 were dramatically better than those for the preceding decade (1971–82). Probable causes for this improvement are the use of surgery at an early age, increase in the experience with the technique, improved perioperative care, better selection of the patients (with exclusion of those with severe pulmonary hypertension that does not decrease in the hyperoxia and tolazoline tests), and general improvement in the care of patients with Down's syndrome. Despite the high mortality of surgery in our study, the outlook is still better with surgery than without. The surgical mortality reported in other series ranged from 62% to 17%.[12 19] Complete atrioventricular canal without major associated intracardiac anomalies can now be repaired in infants younger than 2 years in some of the leading centres with an acceptable mortality of 10–25%.[5 7 19–21]

Prospective studies, which are required to evaluate the late results of current surgical practice, need to include more objective functional assessment. Published late non-actuarial mortality after repair of complete atrioventricular septal defect ranges from 2–19% but the duration of follow up varies considerably.[8 12 21] There was a five year survival of about 47% in our children who were subjected to complete correction from 1983 to 1988, and good functional results of the operation. This compares with a poor prognosis both in terms of survival and of quality of life of the patients treated medically. This confirms the expectation, based on the results in other series, that complete repair drastically improves the natural history of this malformation. This also supports the opinion that this correction should be performed at an early age in as many patients as possible.[19–22] Nevertheless, there are still doubts on the long term consequences of dysplasia of the left atrioventricular valve in the surgically corrected patient, stressing the need for monitoring of these patients over a more extended period.[23 24]

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Commentary

In atrioventricular septal defect and other cardiac lesions sufficient relief from the symptoms of cardiac failure, with prevention of secondary changes in the heart and lungs, may not be afforded by medical treatment alone. Early surgical intervention, despite the complexity of the lesion, to induce immediate improvement and minimise long term changes in both myocardial and pulmonary vasculature is the clear message in this paper.

An additional issue raised by the authors relates to the management of children with multiple handicaps. Society today expects that each handicap will be assessed in its own right, and alleviated so as to produce the optimum benefit to the individual. This relates to the overall quality of life and to the ability to make the fullest use of individual talents. No one would question measures to improve the hearing of the deaf child with heart disease (for example, grommets or a hearing aid) or spectacles for a myopic diabetic. But turning the question around and reducing the symptoms imposed by heart disease brings one back to the primary objectives of intervention. If the simple measures of altering a feeding pattern, judicious use of antibiotic treatment, and medical regimes to reduce cardiac failure do not produce the desired affect in the short term, the logical extension of management is to consider timely surgical intervention. The change in well being, self assurance, and independence not just for the individual but for the whole family should be the ultimate goal. It should remain a goal even if life expectancy is unaltered and could be argued if that expectancy were to be marginally curtailed. The long drawn out illness rendered by advancing pulmonary vascular disease, after a disrupted infancy and childhood, is a heavy burden for a family that timely intervention can curtail. However, in some circumstances the quality of life achieved naturally, even if less than normal, may not be capable of improvement by the most expert surgical intervention. The choice for a child with a single (cardiac) handicap, or for the child with multiple handicaps, lies in the assessment of the improved quality of life and the time that is to be sustained both with, and without, the specific type of medical and surgical intervention necessary to achieve as near perfect an anatomical repair with its consequent improved physiology.

Entering into the current decade, economic factors veiled in the term 'medical audit' will take prominence. In hospital terms the cardiac care of a multiply handicapped child may take longer than for a child with a single system defect. The hospital audit, however, should be able to take into consideration the demand or otherwise on the local paediatric, community, and school medical services. The influence of the child's chronic illness or well being to the total family structure and economy merits deep reflection.

Most congenital heart lesions may be improved and some corrected surgically. The extent to which the repair leaves the heart in a normal state depends on the original lesion; many would accept that closure of a persistent ductus arteriosus is the only truly corrective operation. To this the closure of a moderate sized ventricular septal defect and some forms of total anomalous pulmonary venous drainage might also merit the accolade of 'correction'. Myocardial and pulmonary vascular changes may resolve after operation and the site of the original defect become so well endothelialised that no evidence remains.

Consideration of other lesions even as 'simple' as a secundum atrial septal defect, age at presentation, effects on the myocardium secondary to the lesion, and changes in the pulmonary vasculature, however, will determine the long term performance even after successful anatomical repair. Over and above achieving as near perfect anatomic repair and returning normal physiology the long term effects on pulmonary vascular response, myocardial performance, and the late occurrence of arrhythmias will be the indicators of how near perfection has been attained. There will be a spectrum through the varied surgical techniques needed to 'correct' simple lesions, repair the more complex ones (for example, Fallot's tetralogy, atrioventricular septal defects, coarctation of aorta, aortic stenosis, and transposition with no other defect than atrial septal defect), to essentially long term palliation—for example, persistent truncus arteriosus, pulmonary atresia with a ventricular septal defect, complex transposition, and the problems of the univentricular heart. Semilunar and atrioventricular valve replacement should also be considered palliative. Nevertheless substantial clinical improvement allowing a normal life style, though perhaps not athletic prowess, follows the majority of these procedures.

It is this improvement in well being with freedom from breathlessness and fatigue which forms the real objective in attempting to overcome the physiological impairment of congenital heart lesions. This is accompanied particularly by freedom from cyanosis and irritability, a better nutritional state, and less disturbance from intercurrent infections. An important sequel is the improved confidence to achieve a normal daily life for both the parents and child. While this improved quality of life style should enhance longevity, there are many other factors involved, and this attainment is not the sole or even prime motivation. Even with a good immediate result from surgical intervention the duration of its benefit will be influenced by the state of the myocardium after the operation (itself influenced by preoperative and perioperative factors) and also the evolution or resolution of pulmonary vascular changes. The inherent unavoidable sequelae such as the need to replace a prosthetic valve or renew a conduit (with or without a valve) will also affect ultimate prognosis. Although significant reduction in susceptibility to infective endocarditis is usually listed as a benefit, rarely is the risk eliminated and prosthetic endocarditis can be even more devastating.

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How curable is relapsed Wilms' tumour?

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Abstract

Three hundred and eighty one children with Wilms' tumour were treated on the United Kingdom Children's Cancer Study Group WT1 Study (1980/6). Seventy one patients relapsed during or after treatment, which included surgery and chemotherapy, with irradiation depending on stage and histology. Despite treatment with various combinations of chemotherapy, surgery, and radiotherapy there were only 17 survivors. For unfavourable histology, any stage, only two of 20 survive. We conclude that, after relapse, even for patients who have had localised disease and favourable histology, the 'salvage' rate is little more than 50% and for all others the likelihood of cure is very small. Three of 41 children who relapsed less than 12 months from diagnosis survive, compared with 14 of 30 who relapsed later. It is essential that even with this 'good prognosis' tumour initial treatment is optimal and given by centres experienced in management of children's cancer. Furthermore, there is a clear need for additional effective chemotherapeutic agents for relapsed patients.

Over 85% of patients with Wilms' tumours are cured by conventional combinations of treatment including surgery, radiotherapy, and chemotherapy.[1–3] Most recurrences are within two years of diagnosis, although metastases have developed as long as 11 years after initial treatment.[4 5] Wilms' tumour can recur locally or in several other sites including elsewhere in the abdomen, the contralateral kidney, lungs, liver, bone, and brain. However, the most frequent site of recurrent disease is the lung.[6] Although successful treatment of recurrent disease has been reported for patients with pulmonary metastases[7 8] and for patients with a solitary metastasis in liver or brain,[9–11] the prognosis after abdominal recurrence or unresectable metastatic disease is still poor.[12]

Because most previous reports have not clearly defined their population, it is difficult to draw conclusions regarding the overall efficacy of second line treatment. An exception to this is a recent study of relapsed disease from the National Wilms' Tumour Study Group.[13] In that series a number of adverse features were evident: unfavourable histology, relapse outside the lung (especially in the previously irradiated abdomen), high initial stage, and more than two drugs given initially. Details of the second line chemotherapy were not given but it was suggested that in those patients who relapsed off treatment, the same standard drugs, such as vincristine, actinomycin D, doxorubicin, and cyclophosphamide, could be used to good effect. This report describes the outcome after 'second line' treatment in an unselected group of patients who relapsed after receiving the United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour regimen (WT1).

At relapse the treatment approach was determined by the individual centre, with no formal guidelines from the UKCCSG. In general early surgical resection of operable disease was performed and adjuvant chemotherapy given, which where possible usually included agents that the patient had not already received. Local recurrences at previously unirradiated sites received 35–40 Gy.

Patients and methods

The UKCCSG Wilms' tumour WT1 study was started in January 1980 and closed to patient entry in May 1986. During this period 381 eligible patients were registered on the study: 118 patients with stage I disease, 67 with stage II, 126 with stage III, 50 with stage IV, and 20 with stage V. The histological subgroup was documented in 358 cases: favourable in 317 and unfavourable in 41 patients.[14]

First line treatment included surgery in all patients and irradiation depending on stage and histology. The radiation policy was as follows: stage I—nil, stage II favourable—20 Gy to flank; and stage III—20 Gy to flank or whole abdomen. Chemotherapy was given every three weeks and comprised vincristine 1·5 mg/m^2 for six months for stage I favourable, vincristine and actinomycin D 1·5 mg/m^2 for six months for stage II favourable, vincristine, actinomycin D, and doxorubicin 40 mg/m^2 for 12 months for stage III and stage IV favourable, and vincristine, actinomycin D, doxorubicin, and cyclophosphamide 600 mg/m^2 for 12–15 months for stage IV favourable and all stages with unfavourable histology. All received vincristine weekly (10 doses initially) either alone or in combination.[3] Stage IV treatment was individualised.

At the time of relapse, disease in the lungs was assessed by posterior-anterior and lateral radiography or computed tomography of the chest, or both; in the abdomen by computed tomography or ultrasound examination, or both; in the skeleton by radiography or bone scan, or both; and disease in the brain was detected by computed tomography.

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Table 1 Stage of disease at presentation, initial histology, and survival of the 71 patients who relapsed on the UKCCSG WT1 protocol

Stage of disease	*No of patients*	*No with favourable histology*	*Survival (No patients)*	*No with unfavourable histology*	*Survival (No patients)*
I	11	9	6	2	1
II	11	10	5	1	0
III	23	11	0	12	1
IV	21	16	3	5	0
V	5	5	1	—	0
Total	71	51	15	20	2

Table 2 Treatment given after relapse (n=71)

Treatment	*No of patients*
Surgery	2
Radiotherapy	3
Chemotherapy	22
Surgery/chemotherapy	12
Surgery/radiotherapy	1
Chemotherapy/radiotherapy	18
Chemotherapy/radiotherapy/surgery	7
No treatment	6

Results

Seventy one patients relapsed on the UKCCSG WT1 protocol (table 1). At initial presentation histology was favourable in 51 of the relapsed patients and unfavourable in 20. Seventeen patients (24%) have survived disease free for 20–70 months (median 36).

The management of patients at relapse is summarised in table 2. Two patients died soon after relapse without treatment and in four no further treatment was given electively. Two had surgery alone: one had complete removal of lung metastases and the second a contralateral nephrectomy. In most children a combination of treatments was used; however, in 30% chemotherapy alone was used as second line treatment.

Table 3 shows treatment given to the 17 survivors. The majority had many types of treatment. In only two patients was chemotherapy alone used, and in one surgery alone (nephrectomy) was curative.

Most patients initially presenting with low stage disease achieved a second complete remission (14/19) but three of these subsequently relapsed. It should be noted that most of the survivors had had late relapses occurring off treatment (table 3). In patients with stage III and IV disease who had previously received three drug regimens with or without irradiation, response to subsequent chemotherapy was poor and only three of 44 patients survived.

Discussion

Acquiring information about the cure rate after treatment of relapsed Wilms' tumour is difficult because numbers of patients are small due to the high cure rate after primary treatment. Moreover, interpretation of the published studies is complicated by differences in initial treatment and patient selection. Survival after relapse will depend on the initial stage of disease, histology, relapse site, and the timing of relapse.[7 12 13 15] Advantageous features generally include initial favourable histology, extra-abdominal metastases, and relapse occurring late, after cessation of treatment.

Treatment strategy at time of relapse will depend on the nature of initial treatment. In those patients who relapse off treatment having received only one or two agents, often vincristine alone or vincristine and actinomycin D, it is appropriate to use drugs such as doxorubicin and cyclophosphamide and, where suitable, radiotherapy. By contrast, patients who had more advanced disease will have initially received most conventional active agents, and may have also been irradiated, and new drugs were therefore required. This analysis demonstrates, however, that outcome was disappointing even in patients who originally had low stage disease and who had received only one or two drugs in their initial regimen, suggesting that some degree of cross resistance exists between the original and subsequently used drugs. It should be noted that all the stage I patients who failed

Table 3 Clinical details of patients who survived

Stage at presentation	*Histology*	*Site of recurrence*	*Time of relapse (months after diagnosis)*	*Treatment*			*Survival* (months)*
				Chemotherapy	*Radiotherapy*	*Surgery*	
I	Favourable	Lung	24	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	–	+	35
I	Favourable	Kidney	17	Vincristine, actinomycin D, doxorubicin	–	+	52
I	Favourable	Lung	8	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	–	+	53
I	Favourable	Lung	12	Vincristine, actinomycin D, doxorubicin	+	–	40
I	Favourable	Lung	12	Ifosfamide, actinomycin D, doxorubicin	–	–	43
I	Favourable	Kidney	13	Vincristine, actinomycin D, cyclophosphamide, doxorubicin	–	+	20
I	Unfavourable	Brain	58	—	+	+	28
II	Favourable	Lung+mediastinum	26	HDM, vincristine	+	–	70
II	Favourable	Lung+pericardium	20	Vincristine, actinomycin D	+	–	55
II	Favourable	Liver	16	Ifosfamide, vincristine, doxorubicin	–	–	26
II	Favourable	Pleura	13	Ifosfamide, etoposide, cyclophosphamide, vincristine, epirubicin	–	+	28
II	Favourable	Lymph node	4	Actinomycin D, ifosfamide, vincristine, teniposide	+	+	37
III	Unfavourable	Bone	33	Carboplatin, etoposide	+	–	25
IV	Favourable	Lung	54	Etoposide, cisplatin	+	–	29
IV	Favourable	Lung	19	Ifosfamide, HDM, vincristine	+	–	40
IV	Favourable	Lung+liver	5	Ifosfamide	–	+	40
V	Favourable	Kidney	13	—	–	+	64

*Survival at May 1989.
HDM, high dose melphalan.

second line treatment had relapsed less than 12 months from diagnosis. Such 'multidrug resistance' in the absence of prior exposure is now well recognised and may involve vincristine, actinomycin D, and doxorubicin.[16]

Information regarding activity of drugs other than vincristine, actinomycin D, doxorubicin, and cyclophosphamide is scanty.[17–19] Encouraging response rates with the cyclophosphamide analogue ifosfamide have been reported.[20–22] Unfortunately, the renal toxicity of this drug is causing increasing concern with reports of renal tubular dysfunction.[23 24]

Because of its nephrotoxicity, there are few studies of cisplatin in Wilms' tumour and the results have been disappointing.[20] Carboplatin, the comparatively non-nephrotoxic analogue of cisplatin, is currently under evaluation.

Etoposide has been studied as a single agent and has clear activity in refractory Wilms' tumour.[25] The main toxicity of this drug is myelosuppression and it therefore has advantages over the alkylating agents and anthracyclines, which may have undesirable late effects on fertility and cardiac function, respectively.

The importance of children with cancer being managed at experienced centres has been demonstrated[26] and applies to Wilms' tumour as much as any other tumour.[27] The relative simplicity of the chemotherapy regimens and high cure rates do not mean that paediatricians, surgeons, or radiotherapists can afford not to refer children for specialist care.

Our study demonstrates that although second line treatment is moderately effective in a proportion of patients relapsing after treatment for localised Wilms' tumour, for most children there is no 'second chance'. There is clearly no room for complacency and new drugs or alternative ways to use conventional agents are required.

Patients with initial stage III and IV disease, those with unfavourable histology, or those relapsing less than 12 months after diagnosis should be considered for trials with initial single agent treatment. In this way antitumour activity is determined and the new drug can be included in subsequent combination regimens if effective. This strategy has been applied in the UK and Europe to ifosfamide, etoposide, and currently to carboplatin, and new front line combinations have been logically devised. Although the overall relapse rate is low, there may be scope for improving refinement of prognostic features so that more intensive treatment may be given to those patients at comparatively high risk of relapse.

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Pharmacokinetics of paracetamol after cardiac surgery

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Abstract

Plasma concentration was measured after rectal and nasogastric administration of paracetamol 15 mg/kg to 28 febrile children aged between 9 days to 7 years who had undergone cardiac surgery. After equivalent doses, rectal administration in neonates and children on the first postoperative day was found to produce plasma concentrations below the therapeutic range with higher concentrations after nasogastric paracetamol on the second postoperative day. There was less variance in plasma paracetamol concentrations in neonates. Both plasma elimination half life and area under the plasma concentration time curve were significantly increased in neonates after suppository dosing compared with older children. There was no difference in antipyretic effect between the two routes of administration, but this was much lower than that previously reported in febrile children.

Awareness of the possible role of aspirin in the aetiology of Reye's syndrome and its subsequent withdrawal from everyday paediatric practice has led to an increasing reliance upon paracetamol as the simple analgesic and antipyretic of choice in children. In some situations oral treatment may be inappropriate and rectal administration by suppository has been shown to be an effective and practical alternative.[1 2] Situations in which the rectal route may be chosen include those patients whose clinical condition precludes oral treatment, for example, children who have recently undergone major surgery.

The administration of paracetamol may be necessary in the postoperative period for either its analgesic or antipyretic effects or both. Much recent interest has centred upon safe and efficient forms of postoperative analgesia in neonates, and paracetamol may have a role after some forms of surgery.[3]

An abnormally high body temperature is commonly found during the first 24–48 hours after cardiac surgery. The cause for this is unknown but harm to the patient may be expected to become more likely with increasing temperature as a result of increasing myocardial oxygen demand. At temperatures above 41°C severe and permanent damage to the central nervous system can occur. A recommended scheme of management for postoperative fever in paediatric cardiac surgical patients is paracetamol suppositories every four hours in a dose of 10 mg/kg when rectal temperature exceeds 38·3°C.[4]

Little is known about the pharmacokinetics of paracetamol in young children, particularly in those who are severely ill. Pharmacokinetic studies in healthy adults show plasma elimination half life ($t\frac{1}{2}\ \beta$) to be 2·5 hours after oral and intravenous administration with a reduced bioavailability after oral dosing, possibly due to 'first-pass' metabolism.[5] The bioavailability of the rectal preparation is approximately 80% of that of the oral formulation.[6]

Investigations in neonates have thus far been limited to urinary excretion studies in small numbers of healthy patients. Various authors report differing values, finding $t\frac{1}{2}\ \beta$ to be prolonged in neonates at 3·5 hours compared with 1·9–2·2 hours in children and adults[7] or with no significant difference between mean $t\frac{1}{2}\ \beta$ in neonates (4·9 hours), children (4·5 hours), and adults (3·6 hours).[8] Data from two cases of maternal paracetamol overdose in which delivery took place soon after have shown gross prolongation of $t\frac{1}{2}\ \beta$ in neonates of 10 hours and 26 hours.[9 10]

Estimates of $t\frac{1}{2}\ \beta$ based upon measurement of plasma concentrations after oral administration in children range from a mean of 2·15 hours[11] to 2·3 hours.[12] It has also been shown that accumulation of paracetamol may occur when doses are repeated in infants and children at regular intervals for more than 24 hours.[12] Despite the comparatively low level of activity of the cytochrome *P*-450 system in small infants cases of paracetamol toxicity have been described. Neonates are capable of forming the reactive intermediate that causes hepatocellular damage.[13 14]

We are unaware of any previous studies comparing plasma concentrations in children dosed by the oral and rectal routes after major surgery. This study was therefore designed to investigate the plasma concentrations of paracetamol achieved by rectal and nasogastric doses given to children after major cardiovascular surgery, and to see whether any age dependent differences in pharmacokinetic parameters exist under these circumstances.

Patients and methods

Twenty eight patients who had undergone cardiac surgery took part in the study. The protocol was approved by the ethical review committee of the Royal Liverpool Children's Hospital and informed parental consent was obtained. The children were divided into three groups by age: neonates (up to 1 month), infants (1 month to 1 year) and children (1 to 7 years). Patients were excluded if they had

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received paracetamol within the previous 16 hours or if their plasma bilirubin concentration was raised at the time of the study.

Most patients were in the early postoperative stages of cardiac surgery and at the time of the study were in a state of cardiovascular stability and were being artificially ventilated in the intensive care unit. They were all receiving a number of drugs including morphine, midazolam, vecuronium bromide, antibiotics, inotropes, and vasodilators. The infants and children had undergone a variety of procedures using cardiopulmonary bypass, but owing to the comparatively small number of neonates for open heart surgery, we included five patients who had closed cardiac procedures. These patients, however, were sick enough to require invasive cardiovascular monitoring.

A dose of paracetamol was given rectally on the first postoperative day if the rectal temperature was greater than 38·3°C, the dose used being as close to 15 mg/kg as the available strengths of suppository would allow. Before its administration a 0·5 ml blood sample was taken from the arterial line and subsequently at 30, 60, 90, 120 minutes, 3, 4, 5, 6, and 8 hours. Evidence of expulsion of the suppository was sought throughout the study period. McCarthy's paracetamol suppositories were used. These are made up in a triglyceride base and are available in strengths of 125 and 250 mg (OS-IL, Suppocir Ltd). The 62·5 mg suppositories were made up in the hospital pharmacy by accurately dividing a 125 mg suppository by weight.

On the second postoperative day, providing bowel sounds were present, the process was repeated with paracetamol via a nasogastric tube. The dose used was 15 mg/kg given to the nearest 12 mg (that is, 0·5 ml of Calpol (Calmic) infant suspension 120 mg in 5 ml). After collection the samples were centrifuged and the separated plasma stored at −20°C until assayed for paracetamol. The assay used was the Acetaminophen TDx assay. This is a commercially available fluorescence polarisation immunoassay (Abbott Pharmaceuticals) whose accuracy has been shown over a wide range of concentrations when compared with high pressure liquid chromatography (Abbott Laboratories, data on file). When assaying standard preparations over the range of plasma concentrations encountered, the coefficient of variability of this method in our hands was <5%. Known sources of error with this assay include the presence of unconjugated bilirubin, coumarin anticoagulants, and abnormal concentrations of haemoglobin, lipids, and total proteins, none of which were present in our patients. Assay specificity, allowing for concurrent administration of other drugs, was inferred from the zero results obtained in all cases before administration of paracetamol by either route.

During the study period rectal temperature was continuously monitored with a thermistor probe and temperature recorded at the time of each blood sample.

Pharmacokinetic parameters were calculated from standard formulae. The area under the plasma concentration time curve (AUC) was determined by the linear trapezoidal rule for data points up to 480 minutes, and $t\frac{1}{2}\,\beta$ from the slope of the least squares regression line calculated for data points between 180–480 minutes on a semilog plot of individual plasma concentration against time, assuming an open two compartmental pharmacokinetic model for paracetamol:

$$\beta=2{\cdot}303\times\text{slope, and } t\tfrac{1}{2}\,\beta=0{\cdot}693/\beta.$$

The maximum plasma paracetamol concentration for each patient was noted (Cmax) as was the time at which each peak occurred (Tmax). The values for AUC and Cmax were normalised for dose before subjecting them to within age group comparison using the Kruskal-Wallis one way analysis of variance and to intergroup comparison using analysis of variance. Interaction between dose, AUC, and Cmax and the effects of dose, AUC, and Cmax on the observed maximum individual fall in temperature, were analysed using linear regression.

Results

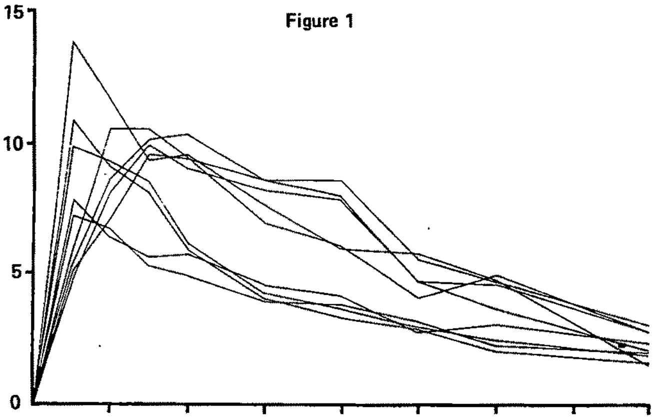
Twenty eight children were studied, and all received a rectal dose of paracetamol on the first postoperative day. It was possible to restudy 13 patients 24 hours later after a nasogastric dose of paracetamol. Because of technical reasons temperature data were only collected from five of the neonates after suppository administration. Retention of suppository occurred in every subject.

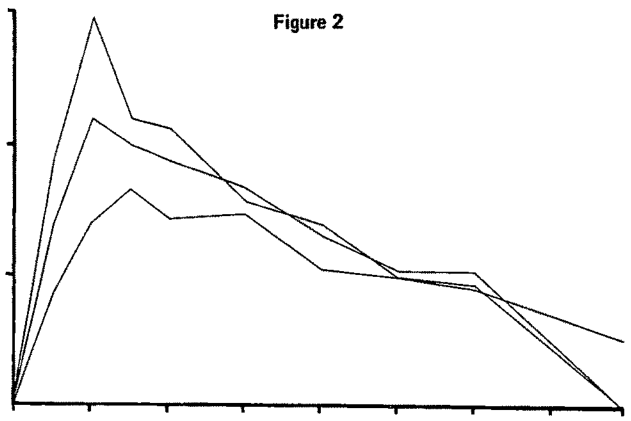
Demographic data and details of doses are given in table 1. Only two of the 28 rectally dosed patients achieved normalised plasma concentrations within the 10–20 µg/ml range. In contrast seven of the 13 nasogastrically dosed patients achieved plasma concentrations in this range.

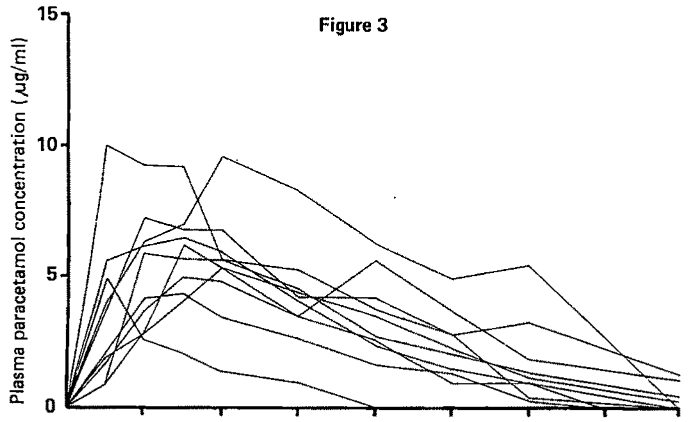
Figures 1 to 6 show individual plasma concentration against time for the three age groups. Summary statistics derived from these are given in table 2. There was no significant difference in AUC between suppository and nasogastric

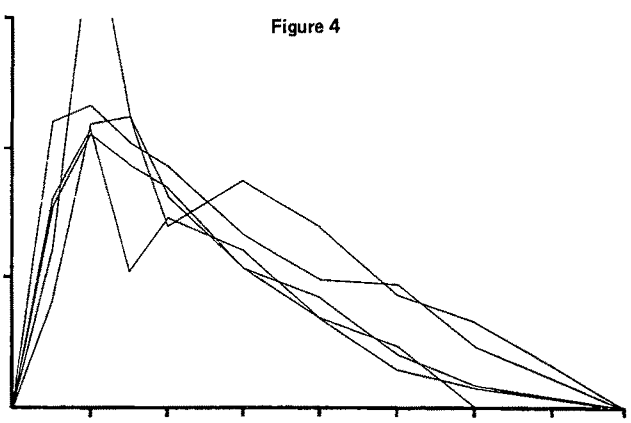
Table 1 Demographic and dose data for all groups. Figures are mean (95% confidence interval)

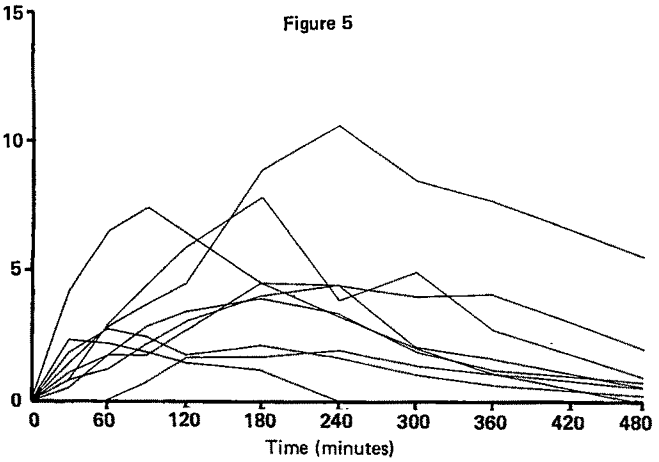
	No of patients	*Sex (M/F)*	*Age*	*Weight (kg)*	*Dose (mg/kg)*
Neonates:					
Suppository	9	6/3	11·8 (6·9 to 16·7) days	3·7 (3·1 to 4·3)	18·1 (15·2 to 21·0)
Nasogastric dose	3	2/1	12·3 (7·3 to 17·3) days	3·3 (2·6 to 4·0)	15·9 (14·4 to 17·4)
Infants:					
Suppository	10	6/4	3·6 (2·3 to 4·9) months	4·2 (3·0 to 5·4)	17·9 (14·6 to 21·2)
Nasogastric dose	5	3/2	4·2 (2·4 to 6·0) months	4·3 (2·6 to 6·0)	19·6 (17·2 to 22·0)
Children:					
Suppository	9	5/4	2·7 (0·8 to 4·6) years	12·4 (9·1 to 15·7)	15·3 (13·0 to 17·6)
Nasogastric dose	5	3/2	2·3 (0·9 to 3·7) years	10·9 (8·2 to 13·6)	14·5 (13·9 to 15·1)











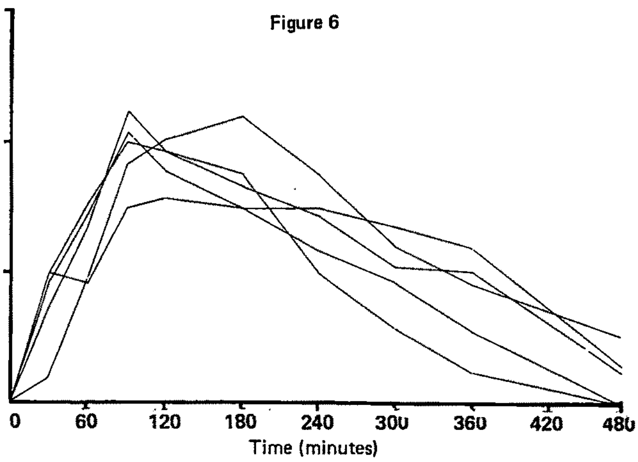


Figure 1 *Plasma paracetamol concentration in neonates after suppository.*

Figure 2 *Plasma paracetamol concentration in neonates after nasogastric dose.*

Figure 3 *Plasma paracetamol concentration in infants after suppository.*

Figure 4 *Plasma paracetamol concentration in infants after nasogastric dose.*

Figure 5 *Plasma paracetamol concentration in children after suppository.*

Figure 6 *Plasma paracetamol concentration in children after nasogastric dose.*

Table 2 Area under curve (AUC), peak plasma concentration (Cmax), time to Cmax (Tmax), and elimination half life ($t\frac{1}{2}\ \beta$) results for all groups. AUC and Cmax normalised to a dose of 15 mg/kg. Figures are mean (95% confidence interval)

	AUC (µg·hour/ml)	*Cmax (µg/ml)*	*Time to Cmax (min)*	*$t\frac{1}{2}\ \beta$ (hours)*
Neonates:				
Suppository	46·3 (37·4 to 55·2)	7·9 (7·0 to 8·8)	58 (22 to 94)	3·8 (2·7 to 4·9)
Nasogastric dose	58·9 (46·0 to 71·8)	11·2 (9·0 to 13·4)	70 (53 to 87)	2·8 (1·2 to 4·4)
Infants:				
Suppository	21·9 (12·8 to 31·0)	5·7 (3·3 to 8·1)	78 (46 to 110)	1·7 (1·0 to 2·4)
Nasogastric dose	30·9 (21·5 to 40·3)	9·7 (6·6 to 12·8)	66 (53 to 79)	1·6 (0·8 to 2·4)
Children:				
Suppository	26·1 (8·0 to 44·2)	5·3 (2·0 to 8·6)	153 (77 to 229)	2·6 (1·4 to 3·8)
Nasogastric dose	56·0 (42·1 to 69·9)	10·5 (9·0 to 12·0)	114 (75 to 153)	2·3 (1·8 to 2·8)

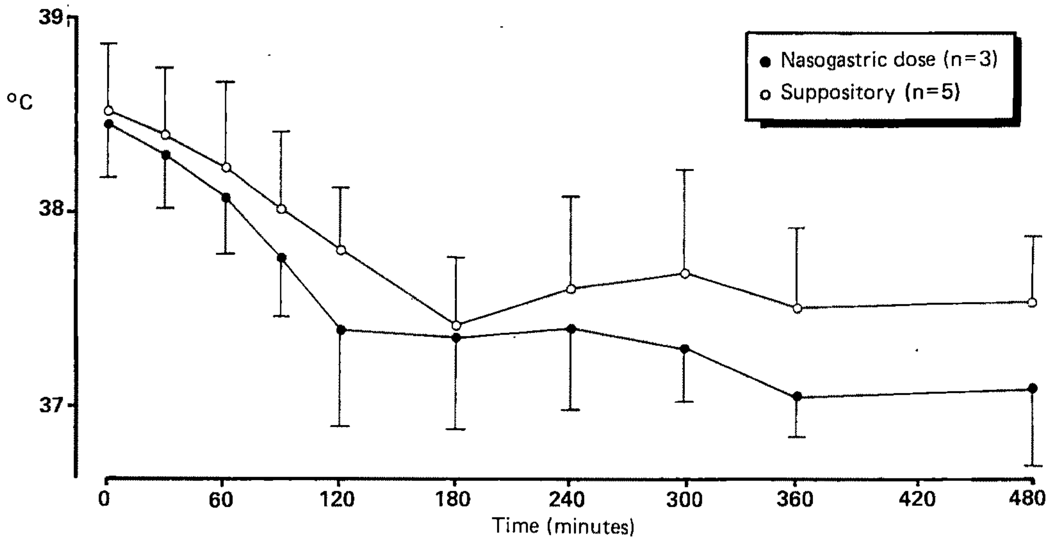


Figure 7 *Mean temperature change in neonates after suppository or nasogastric dose (bar is 95% confidence interval).*

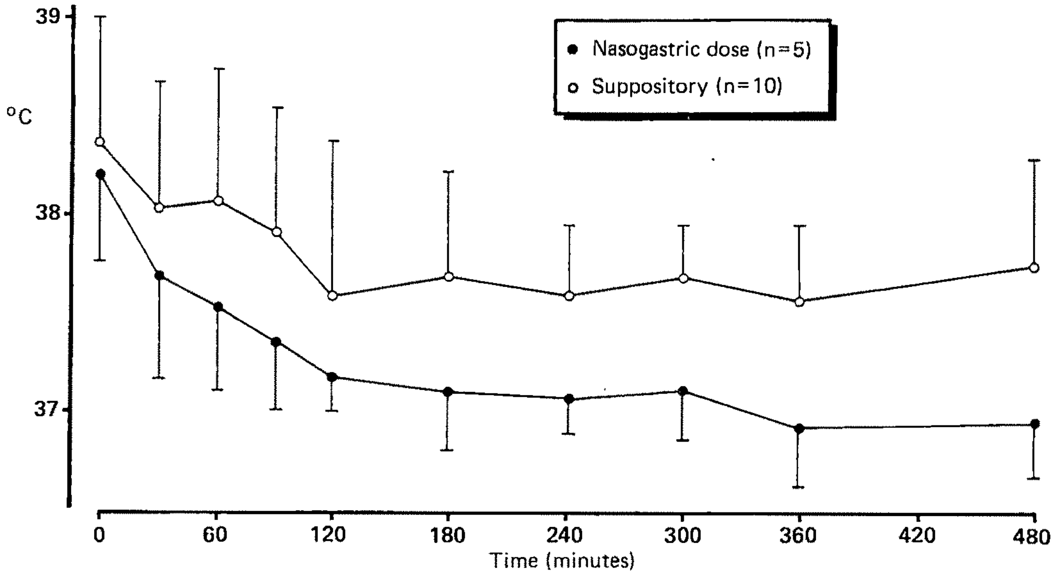


Figure 8 *Mean temperature change in infants after suppository or nasogastric dose (bar is 95% confidence interval).*

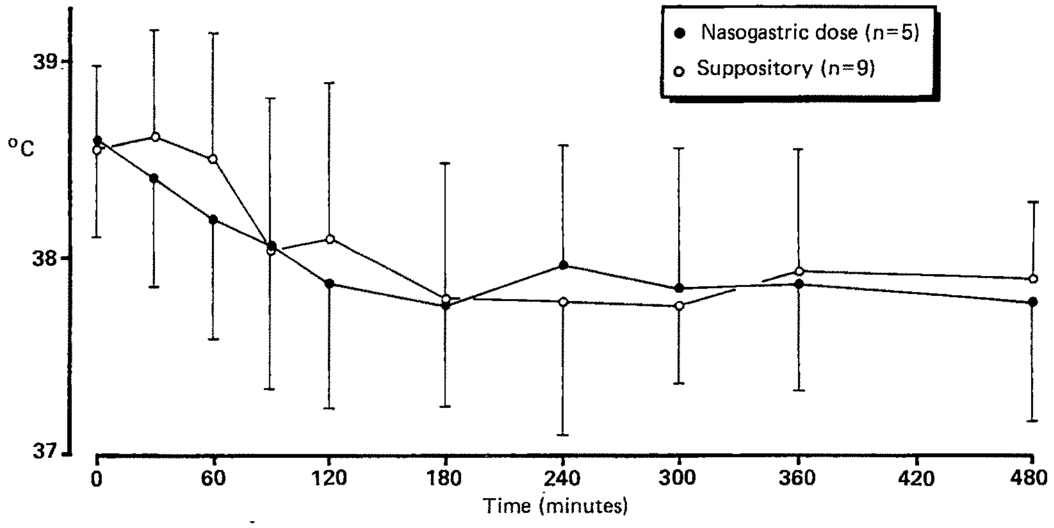


Figure 9 *Mean temperature change in children after suppository or nasogastric dose (bar is 95% confidence interval).*

routes in neonates and infants. The mean AUC value in children after suppository was significantly lower than after nasogastric dosing (Kruskal-Wallis test H=6·76, df=1, p=0·009). The AUC in neonates after suppository was significantly greater than in infants or children (F ratio 9·8, p=0·00099). The AUC in children after nasogastric dosing was significantly lower than in neonates and children (F ratio 7·24, p=0·011). For AUC results after suppository combining all groups there was a significant correlation with dose thus:

AUC (μg/hour/ml)=−33·8+3·9×dose (mg/kg) r=0·58, p=0·003

Cmax values were significantly lower after suppository compared with nasogastric dosing in neonates (H=5·72, df=1, p=0·016) and children (H=4·27, df=1, p=0·037). There was no significant difference in Cmax values between age groups.

There was no significant difference within groups for time to maximum plasma concentration Tmax and for t½ β. The time to maximum plasma concentration was significantly prolonged in children after both suppository (F=8·73, p=0·0016) and nasogastric dosing (F=4·49, p=0·039). The t½ β was significantly prolonged in neonates after suppository dosing (F=9·75, p=0·001) but there was no significant difference between age groups after nasogastric dosing.

Figures 7 to 9 show mean changes in temperature for the three groups. Summary statistics of maximum individual fall in temperature were obtained and there was no significant correlation between Cmax, dose, AUC, and maximum temperature fall. Temperature reduction occurred in all groups with no significant differences within or between groups.

In all patients paracetamol concentrations were zero before commencing the study and results of liver function tests remained normal throughout.

Discussion

(1) SAFETY

Our results confirm the safety of single doses of paracetamol in this group of patients. Liver toxicity is likely if the plasma paracetamol concentration exceeds 120 μg/ml four hours after ingestion.[15] In none of our patients did plasma paracetamol exceed 20 μg/ml at any time after doses of up to 25 mg/kg.

(2) LOW (SUBTHERAPEUTIC) CONCENTRATIONS

The effective plasma concentration of paracetamol for analgesia and antipyresis is quoted as 10–20 μg/ml.[15] In our patients nasogastric paracetamol on the second postoperative day proved to be a more predictable means of achieving these concentrations than equivalent rectal doses given on the first postoperative day. The peak plasma concentrations after paracetamol suppositories were higher than those of 4·0 (SD 1·6) μg/ml previously described after a (lower) dose of 10 mg/kg by suppository in nine children aged 7–12 years.[11] The peak plasma concentrations after nasogastric administration are similar to those in another study with peaks of 9·96–19·6 μg/ml after 12–14 mg/kg of paracetamol elixir.[12] The delay in achieving peak plasma concentrations in the older children after nasogastric dosing could be due to delayed gastric emptying as more of these patients were receiving opiates, which are known to decrease the rate of absorption of paracetamol.

The mean falls in temperature which we found were considerably less than in two previous studies comparing the antipyretic effects of oral and rectal paracetamol in febrile children.[1 2] Their patients showed a range of fall in temperature of between 1·63 and 1·89°C after doses of 15–20 mg/kg paracetamol given rectally or orally. It is possible that the fever that follows cardiac surgery is less amenable to paracetamol treatment than is fever due to infection. The overall finding that plasma concentrations resulting from administration of suppositories were below accepted therapeutic values and that the antipyretic effects were disappointing indicates the need to assess the effects of higher rectal doses upon body temperature. Alternatively, different formulations of paracetamol for rectal use may be associated with greater bioavailability.[1]

(3) PLASMA HALF LIFE (T½ β) (FIG 10)

Mean t½ β in children in this study (2·3 hours) resembles closely that previously found in adults after oral and intravenous administration (2·5 hours).[5] Similarly, t½ β in neonates (3·8 hours) after suppository is close to that previously determined in another urinary excretion study (3·5 hours).[7] The difference between t½ β values for neonates, infants, and children after nasogastric dosing was not significant and this is in agreement with earlier work.[8]

(4) PLASMA CONCENTRATION TIME CURVE (AUC) (FIG 11)

The AUC is dependant upon both bioavailability and drug clearance. The relative bioavailability of oral and rectal paracetamol is known to be <1·0 therefore direct calculation of volume of distribution and clearance from the AUC is invalid. It has also been shown that the bioavailability of paracetamol is dose dependant,

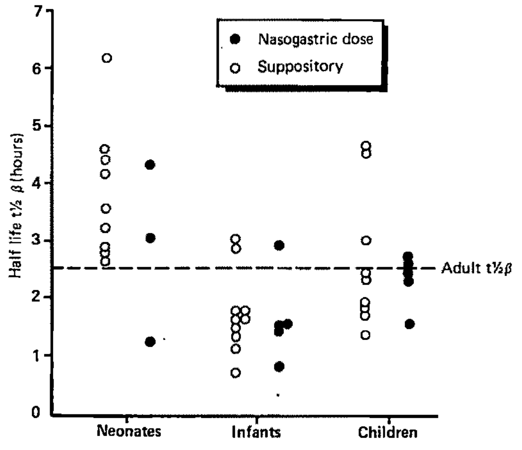


Figure 10 Individual elimination half life (t½ β) for all groups.

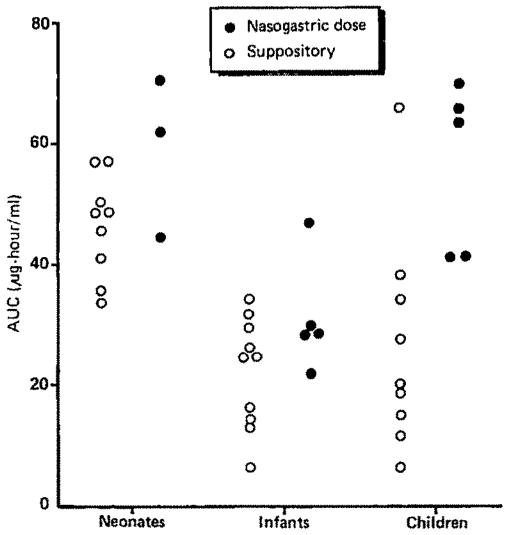


Figure 11 Individual area under curve (AUC) values for all groups.

and has greater variability at higher doses. The design of this study does not preclude an order effect as the suppositories were always administered before the nasogastric dose. There is no evidence from previous pharmacokinetic studies, however, to suggest that this would influence the results we obtained, and this is the sequence that is employed in clinical practice.

In summary, caution should always be employed when translating the results of pharmacokinetic studies to the clinical situation. We believe that the low absolute paracetamol concentrations may explain the disappointing clinical effect in our patients, although it is also possible that the fever which follows cardiac surgery is less amenable to paracetamol treatment than is fever due to infection.

It is apparent from this study that triglyceride based suppositories in a dose of 15 mg/kg may produce plasma concentrations that are subtherapeutic, but also nasogastric administration in children who have received opiates may be no more effective. The pharmacokinetic values are in agreement with previous findings. We believe that further studies are needed to see whether there is any tendency for paracetamol to accumulate in neonates after regular dosing with suppository in view of the prolonged half life, and to assess the response to increased dosing with suppository in older children. In the meantime, as one method of urgently reducing a child's temperature shortly after major surgery, if the oral route is not available, we would recommend a single triglyceride based suppository in a dose of 20–25 mg/kg as being safe and possibly more effective than previously recommended doses.

We wish to thank Andrew Johnson, MLSO at Myrtle Street Children's Hospital, for performing the estimation of paracetamol concentrations and Abbott Diagnostics for supplying the TDx Paracetamol assay reagents.

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Plasma prolactin and clinical outcome in preterm infants

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Abstract

Plasma prolactin was measured weekly in 280 preterm infants. The complex gestational age dependent pattern of postnatal prolactin release has been defined and reference standards provided. Plasma prolactin was higher in girls, with increasing divergence between the sexes from the third week onwards, and higher after two weeks, in infants of mothers with pregnancy related hypertension. Diet, assigned randomly, exerted a major effect on plasma prolactin, with significantly higher values in infants fed donor breast milk or standard formula than in those fed a protein, energy, and mineral enriched preterm formula. After adjusting for confounding factors, infants with the lowest plasma prolactin concentrations (<1000 mU/l, 32·9 μg/l) occurring usually at a nadir between days 5 and 12, showed a 120% increase in the duration of ventilatory assistance required, a 20% increase in the number of days to attain full enteral feeds, and a 30% decrease in length gain.

We suggest preterm birth disrupts the normal perinatal pattern of prolactin release and that those infants who develop relatively low plasma concentration have an adverse outcome. Our data add to the broader debate on whether preterm infants require multiple endocrine replacement treatment.

Prolactin has a central role in stimulating milk production. Numerous and diverse actions for prolactin have been proposed in animals and man, however,[1 2] and in recent years the possibility has been raised that prolactin is important for developmental events in the perinatal period.[3–7]

High plasma prolactin concentrations are found in the fetal circulation and in amniotic fluid.[5 8] Plasma values considerably in excess of those seen in adults have been found in neonates and persist up to three months postnatally in full term infants and longer still in infants born preterm.[9–11] Prolactin may be important for lung maturation and surfactant synthesis,[12–17] and the possibility that low plasma concentration might be of aetiological importance in hyaline membrane disease in preterm infants has been suggested and debated by several groups.[7 12–15 18–22] Further evidence, also debated, points to a possible role for prolactin in the growth of the gut and its mucosal function[23–25] and the intestinal absorption of fluid and ions.[26]

Because of the uncertainty about the physiological actions of prolactin in early life and its potential importance in preterm neonates, we have studied plasma prolactin concentrations longitudinally in a large cohort of intensively monitored premature infants, taking part in a multicentre feeding trial.[27] Firstly, we have derived standards for plasma prolactin concentrations, taking into account postnatal age, gestation, and sex. Secondly, we have investigated the effect of diet and possible influence of other perinatal factors on prolactin release. Finally, in view of the observations above, we have explored, using regression analysis to adjust for confounding factors, whether postnatal plasma prolactin concentrations relate to selected clinical outcome responses potentially linked to the development of the lung or gut. These outcomes include duration of severe respiratory disease, necrotising enterocolitis, days to attain full enteral feeds, and growth performance.

Subjects and methods

Longitudinal data derived from a large multicentre infant feeding study were analysed.[27] A total of 280 neonates were studied in five centres with a mean (SE) gestational age of 30·3 (0·2) weeks and a mean birth weight of 1330 (18) g. All were less than 1850 g at birth. Extensive data were collected on their biochemical profiles. Growth data were collected as described previously.[27]

In three centres infants whose mothers elected not to provide their own milk were assigned randomly[27] to receive either banked pooled donor breast milk or a preterm formula (Oster-Prem, Farley Health Products) as sole diets (trial 1). When mothers expressed their own 'preterm' milk the infants were assigned randomly to receive either donor breast milk or preterm formula as supplements in volumes according to the mother's success in expressing her milk (trial 2). In the remaining two centres infants were assigned randomly to receive either a standard 'term' formula (Osterfeed, Farley Health Products) as sole diets (trial 3) or as supplements to mothers milk (trial 4). The protein, energy, and sodium contents of the preterm formula were: 2·0 g/100 ml, 0·33 MJ (80 kcal)/100 ml, and 19·6 mmol/l, and of the standard formula: 1·45 g/100 ml, 0·28 MJ (68 kcals)/100 ml, and 8·3 mmol/l, respectively.

In each subject plasma prolactin was measured weekly until discharge from hospital or until a weight of 2000 g was exceeded; the mean (SD) duration in study was 37·3 (20·6) days. Data beyond week 7 are presented as the mean of values from week 8 onwards for each subject still in the study. The population of infants remaining in the study fell with postnatal age; of the 280 subjects, 160 remained beyond week 4 and 56 beyond week 8. An additional cross sectional analysis was performed on values obtained within two day blocks of time from days 1–2 up to day 13–14.

Venous samples were collected in cooled heparinised tubes, centrifuged at 4°C, and the plasma fraction stored at −20°C within 30 minutes of sampling. Plasma prolactin concentrations were measured on 1340 duplicate 20 μl samples by radioimmunoassay (CIS France). The percentage cross reactions obtained by the assay were: prolactin 100%, human growth hormone 0·24%, and human placental lactogen, luteinising hormone, follicle stimulating hormone, human chorionic gonadotrophin, and thyroid stimulating hormone×10^{-4}%. Minimum assay sensitivity was 26 mU/l (0·85 μg/l).

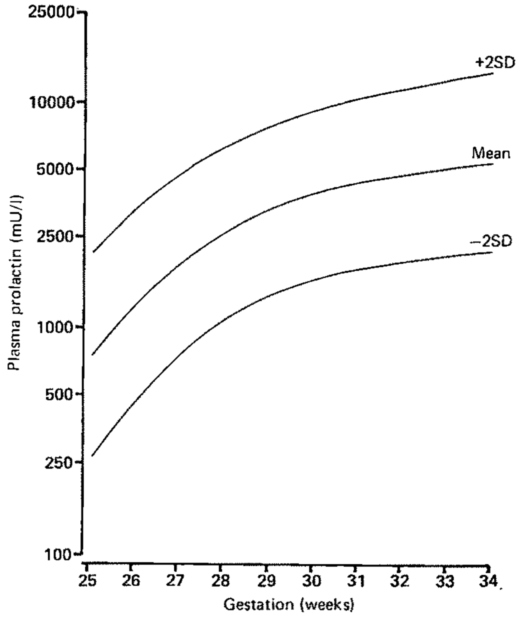

Figure 1 Plasma prolactin (plotted on a logarithmic scale) in preterm neonates during the first 48 hours at gestations from 25 to 34 weeks. Data have been smoothed and represent the geometric mean±2SD. To convert mU/l to μg/l divide by 30·4.

Statistical analyses were performed using Student's t test and χ^2 tests; multiple and logistic regression was used to explore the association between plasma prolactin concentrations and a range of perinatal and neonatal factors. For these analyses, plasma prolactin has been treated either as a dichotomous variable (a value above or below a given threshold) or as a continuous one. In the latter case, as data were postively skewed, they were analysed after log transformation. For presentation, data have been antilogged, providing geometric means with 95% confidence intervals.

Results

REFERENCE VALUES FOR PLASMA PROLACTIN IN PRETERM INFANTS

Plasma prolactin concentrations in the first 48 hours after birth were strongly related to gestation (fig 1 shows a smoothed reference chart). At 25–26 weeks plasma prolactin was 950 mU/l (31·3 μg/l) (95% of values lying between 340 (11·2) and 2660 (87·5)) rising to 5420 (178·3) (2120 (69·7), 13840 (455·3)) mU/l (μg/l) at 33–34 weeks ($p<0\cdot001$).

Table 1 shows smoothed reference values for plasma prolactin in the first seven weeks according to gestation. Early values, up to 14 days, are for both sexes combined, because as shown below, consistent sex differences do not emerge until later in the neonatal period. In each gestational age group plasma prolactin concentrations fell postnatally to a nadir at a mean of seven to 10 days followed by a rise. The overall trend in plasma prolactin over the first seven weeks depended on gestation (table 1 and fig 2A). In infants under 28 weeks, after an initial fall ($p<0\cdot001$), values rose progressively over the next six weeks ($p<0\cdot001$). In contrast (fig 2A) infants of 32–36 weeks' gestation showed overall a major fall in plasma prolactin from birth to week 7 ($p<0\cdot001$).

Figure 2B shows sex differences in plasma prolactin for the whole cohort. In the first 48 hours, values were lower in boys 2440 (80·3)

Table 1 Plasma prolactin concentrations in mU/l in preterm infants in the first seven weeks according to gestational age and sex. For the period 1–14 days and in infants under 28 weeks' gestation both sexes are combined. Data were originally log transformed to derive means and SDs; the data here have been antilogged to provide a geometric mean plus or minus 2 SD*

Postnatal age	25–27 Weeks' gestation (n=36)			28–31 Weeks' gestation (n=152)			32–36 Weeks' gestation (n=92)		
	−2SD	Mean	+2SD	−2SD	Mean	+2SD	−2SD	Mean	+2SD
Day:†									
1–2	350	1620	7590	870	3020	10470	2240	5370	12880
3–4	270	910	3090	680	2400	8510	1150	2820	6920
5–6	190	630	2140	590	2040	7080	810	2140	5620
7–8	180	580	1860	540	1820	6170	710	2000	5620
9–10	200	630	2000	510	1700	5620	720	2140	6310
11–12	300	830	2290	650	1910	5620	790	2340	6920
13–14	360	980	2690	910	2400	6310	910	2690	7940
				28–36 Weeks' gestation combined‡					
				Boys (n=120)			Girls (n=124)		
Week:									
3	410	1180	3390	760	1910	4790	680	2340	8130
4	510	1480	4270	660	1700	4370	710	2290	7410
5	530	1510	4570	590	1510	3890	780	2340	7080
6	520	1620	5010	490	1320	3550	810	2340	6760
7	550	1700	5250	430	1180	3240	870	2340	6310

*To convert mU/l to μg/l divide by 30·4.

†As subjects provided one sample/week, data for days 1–14 are based only on those subjects who were sampled in each two day time period (about one third of subjects sampled/two day period).

‡From week 3, infants of 28–31 and 32–36 weeks' gestation have been combined as there were no significant differences between these groups after this age.

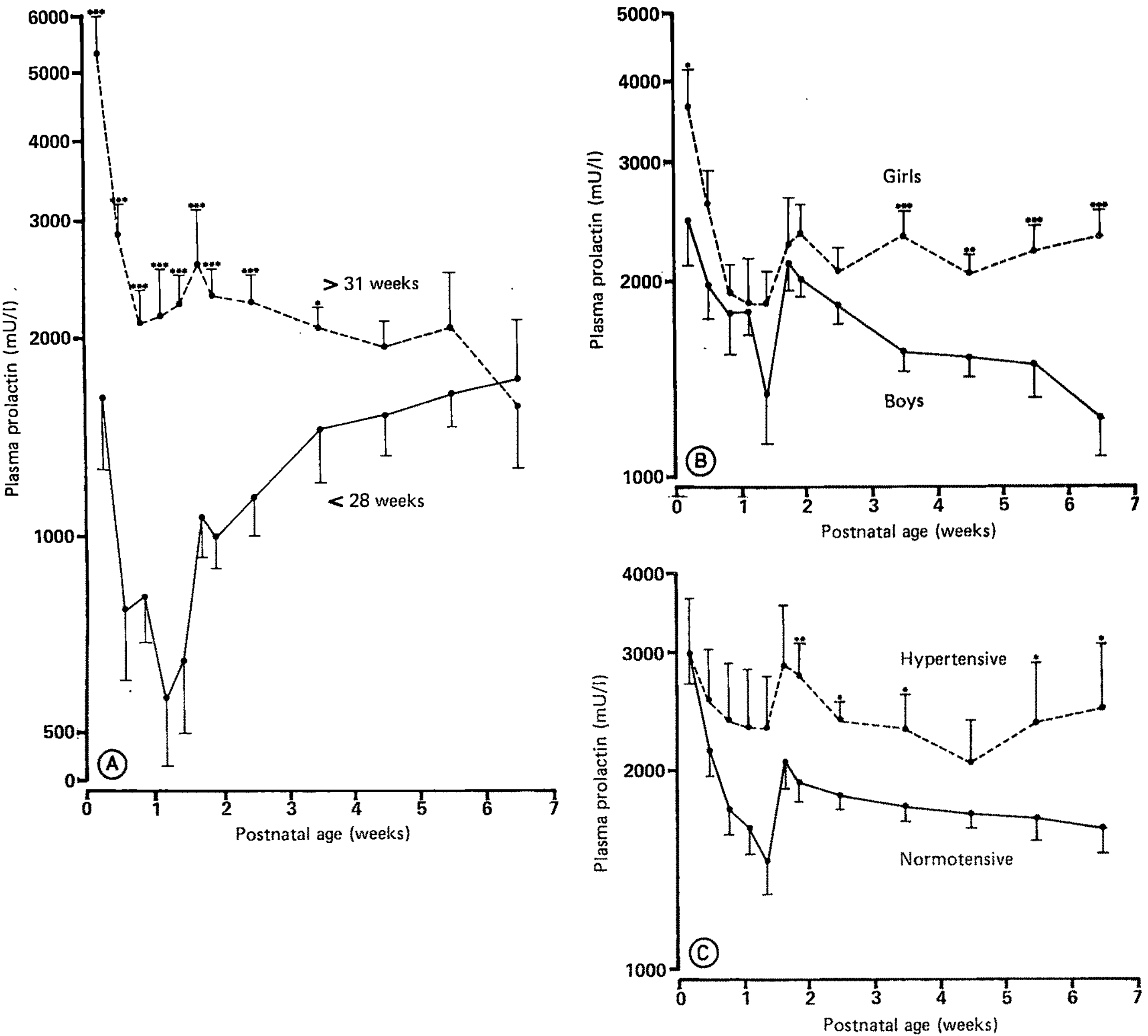

*Figure 2 Plasma prolactin in preterm infants during the first two months: (A) infants under 28 weeks compared with those above 31 weeks' gestation; (B) boys compared with girls; and (C) infants whose mothers had pregnancy related hypertension compared with those with normotensive mothers. Data are geometric mean (SE) ***p<0·001; **p<0·01; *p<0·05. To convert mU/l to µg/l divide by 30·4.*

(620 (20·4) to 9600 (315·8)) mU/l (µg/l) than in girls 3600 (120·4) (1100 (36·2) to 12180 (400·7)) mU/l (µg/l) (p<0·5). This difference did not reach significance again until week 3, after which there was a major and progressive divergence in values between the sexes.

FACTORS RELATING TO PLASMA PROLACTIN CONCENTRATIONS

In addition to gestation and sex, a range of other factors were explored for their association with plasma prolactin.

Effect of diet

Figure 3A shows plasma prolactin in infants in trials 1 and 2. While those fed on breast milk showed no change in prolactin values from the second to seventh week, values in the group fed preterm formula declined progressively and were significantly lower beyond weeks 3. A similar trend was seen in trials 3 and 4 with lower values on preterm formula. The differences (not depicted) did not reach significance in this much smaller comparison. In fig 3B, however, all four trials have been combined to compare infants fed 'unfortified' diets: banked milk or term formula compared with those fed a 'fortified' preterm formula. As this is a balanced addition of trials, the comparison is a randomised one. In infants fed preterm formula, plasma prolactin concentrations declined linearly (p<0·01) with values progressively diverging from those seen on banked milk or standard formula.

As high prolactin concentrations are found in early milk,[28] we considered that these might contribute to high plasma concentrations in newborn infants. A comparison of infants fed 90% or more of their own mothers early preterm milk with infants fed on mature donor breast-

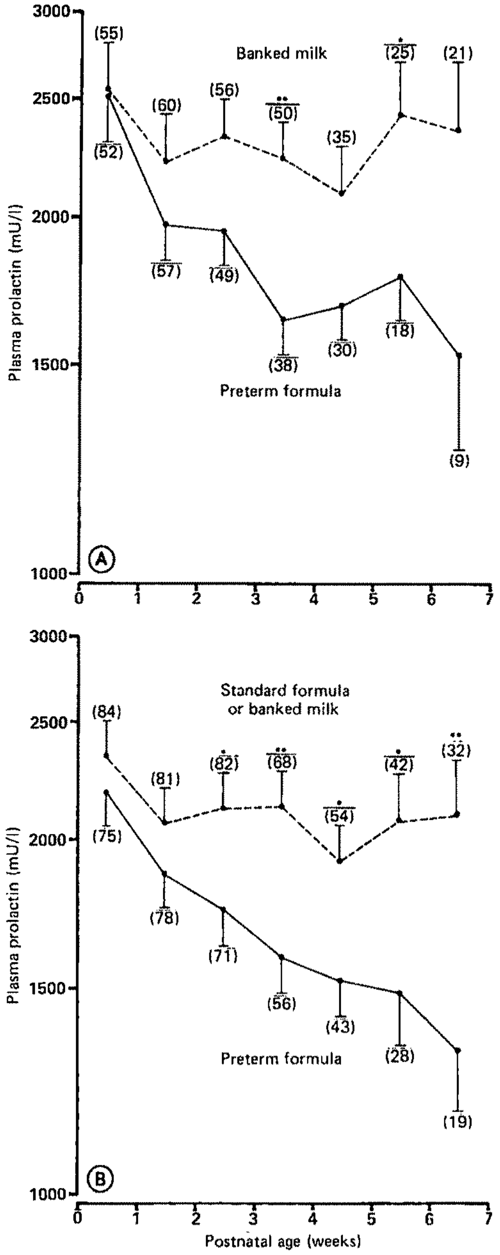

*Figure 3 Effect of diet, randomly assigned, on plasma prolactin concentration in preterm infants during the first two months. (A) Banked donor breast milk compared with preterm formula, as sole diets or supplements to maternal milk and (B) standard formula or banked milk ('unfortified diets') compared with preterm formula as sole diets or supplements to maternal milk. **p<0·01, *p<0·05.*

milk, however, failed to show any difference in neonatal plasma prolactin (*t* values for the difference at ages 1–3 days and 4–7 days were 0·02 and 0·71).

Other factors

Using regression modelling, a range of factors have been examined for their independent relationship with prolactin concentration, calculated as the mean of all values for each subject in the first month (dependent variable). Independent variables included the infant's sex, gestation (above or below 28 weeks), birth weight, diet (banked milk or standard formula compared with preterm formula), and fetal growth retardation (birth weight above or below 10th centile). Also included were pregnancy related hypertension (diastolic blood pressure 90 mm Hg or over; or systolic blood pressure 140 mm Hg or over), days of mechanical ventilation (log transformed; plus 1, to avoid log 0), Apgar score at five minutes (below 5 compared with 5 and above), mode of delivery (caesarean compared with vaginal), necrotising enterocolitis, number of days to attain full enteral feeds (defined as 150 ml/kg per day or more), and days of dopamine treatment (only eight cases).

Four factors were independently associated with plasma prolactin: sex (higher in girls, p<0·001), gestation (higher above 28 weeks; p<0·001), pregnancy related hypertension (associated with higher values, p<0·02), and diet (lower on preterm formula, p<0·02). Raw data on the association between these four factors and plasma prolactin (against postnatal age) are shown in table 1 and figs 1, 2, and 3.

Interaction terms were also introduced into the models to explore any interactions between gestation, sex, diet, and hypertension. The only one identified was between gestation and hypertension, demonstrating that a significant rise in plasma prolactin in hypertensive subjects was greatest in infants of low gestation. As babies of hypertensive subjects had a slightly higher mean gestation than those of those who were normotensive (31·7 compared with 30·5 weeks), the data depicted in fig 2C represent an underestimate of the difference that would have been seen if the two groups had had the same mean gestation.

In order to explore the possibility that the dietary effect (above) related to sodium status, mean plasma sodium concentration (in week 1 or month 1) was added to the models. No association between plasma sodium and plasma prolactin emerged, and the dietary effect was unchanged.

It should be noted that in all the longitudinal data described above, sample size diminished when the larger babies were discharged from hospital. Thus after the first month the popula-

Table 2 Raw data on association between the minimum (lowest) plasma prolactin concentration in the neonatal period and respiratory disease, prolonged establishment of enteral feeds, and neonatal linear growth rate

	*Minimum plasma prolactin concentration (mU/l)**			
	<1000	*1000–1999*	*2000–2999*	*≥3000*
No (%) infants with respiratory distress syndrome (needing ventilation)	50/67 (75)**	65/128 (51)	26/50 (52)	16/35 (46)
No (%) of infants ventilated >7 days	29/67 (43)***	15/128 (12)	4/50 (8)	2/35 (6)
No (%) infants taking >14 days to full enteral feeds	16/59 (27)*	14/120 (12)	6/49 (12)	4/33 (12)
Mean (SE) length gain (mm/day)	1·09 (0·07)	1·33 (0·06)	1·33 (0·08)	1·33 (0·09)

*To convert mU/l to μg/l divide by 30·4.
†Nineteen of 280 subjects died before attaining full feeds.
***p<0·001, **p<0·01, *p<0·025 for comparison of infants whose minimum plasma prolactin was below 1000 mU/l and all infants whose minimum plasma prolactin was 1000 mU/l and above (last three columns in the table combined).

tion remaining in the study was predominantly infants below 32 weeks' gestation.

ASSOCIATION BETWEEN PLASMA PROLACTIN AND CLINICAL OUTCOME

In a series of regression models, plasma prolactin has been treated as an independent variable to explore its association with the following clinical outcome responses (dependent variables): duration of respiratory disease (days of ventilation), necrotising enterocolitis, days to full enteral feeds (over 150 ml/kg per day), weight gain (g/kg per day), length gain (mm/day), and head circumference gain (mm/day) (the growth rates were assessed from the day of regaining birth weight to discharge from the study). Logistic regression was used for the dichotomous dependent variable, necrotising enterocolitis. Further independent variables were the same as those in the models described in the previous section.

No association was found between mean or the peak (highest) plasma prolactin concentration and any of the outcome responses. After adjusting for confounding factors (above), however, the minimum plasma prolactin concentration, usually occurring between days 5 and 12, was found to be significantly related to duration of ventilation ($p<0{\cdot}005$), linear growth (length gain) in the neonatal period ($p<0{\cdot}02$), and the number of days of full enteral feeds ($p<0{\cdot}03$) (minimum prolactin concentration was log transformed in these models to achieve the best fit).

From inspection of the raw data in table 2, it is apparent that when the minimum plasma prolactin concentration fell below 1000 mU/l (32·9 μg/l) there was a sharp rise in the duration of ventilatory assistance and days to full feeds and a sharp fall in linear growth. Using regression analysis to adjust for confounding factors, a value of 1000 mU/l (32·9 μg/l) again proved to be the best modelled cut off for predicting these adverse outcomes. Plasma prolactin values under 1000 mU/l (32·9 μg/l) in the first week were independently associated with an increase in the number of days of ventilation ($p<0{\cdot}001$), the proportion of subjects ventilated for over seven days ($p<0{\cdot}001$), neonatal length gain ($p=0{\cdot}018$), and the number of days to attain full enteral feeds ($p=0{\cdot}027$) (fig 4).

The raw data (table 2) show that the incidence of respiratory disease as well as the duration was related to low plasma prolactin; after adjusting for confounders (table 3), only the duration was significantly related. Interestingly, despite previous reports that low plasma prolactin at birth relates to the incidence of respiratory distress,[6 7 12] we found no association between plasma prolactin in the first 48 hours and the incidence or duration of respiratory disease. Low plasma prolactin was unrelated to weight gain, head circumference gain, or necrotising enterocolitis.

Table 3 Association between low plasma prolactin (<1000 mU/l) and duration of severe respiratory disease, days to establish full enteral feeds, and linear growth, after adjusting for potentially confounding factors (see text) by multiple regression

Dependent variable	*Plasma prolactin <1000 mU/l**	*95% Confidence interval*	*p Value*
Days of ventilation†	Increased by 2·2:1	1·4:1 to 3·6:1	<0·001
Days to attain full enteral feeds	Increased by 1·2:1	1·0:1 to 1·4:1	0·027
Length gain (mm)	Decreased by 0·33	−0·08 to −0·74	0·018

*To convert mU/l to μg/l divide by 30·4.
†Log transformed for statistical analyses.

Discussion

In a large cohort of preterm infants monitored during the early months we have defined the complex pattern of longitudinal changes in plasma prolactin concentration and provided new reference standards. A major effect of diet on plasma prolactin concentration emerged, and after adjusting for other factors the infant's sex and gestation and pregnancy related hypertension in the mother were strongly related to the pattern of prolactin release. Most important, low plasma prolactin in the neonatal period was significantly related to prolonged respiratory disease, an increase in the length of time taken to establish enteral feeds, and reduced linear growth performance, even after adjusting for a wide range of potentially confounding factors.

Several studies describe hyperprolactinaemia in preterm and term infants,[9–11] but the complexity of the postnatal changes and their relation to gestation and sex had not been adequately defined. Cord plasma values have been shown to rise with gestation.[21] Our data show a sixfold increase in plasma prolactin between 25 and 30 weeks' gestation, from a concentration little above the normal adult reference range. High fetal values, which are believed to derive from the fetal pituitary and not the mother, may be induced by maternal oestrogens.[5] This could explain high plasma prolactin we and others have observed in the early days after birth.[9] We showed that regardless of gestation and in all subgroups studied plasma concentrations fell rapidly to reach a nadir at seven to 10 days, followed by a significant rise by the 12th day and possibly a second smaller fall.

Breast milk contains very high prolactin concentrations in the first three days.[28] Our data did not suggest that this contributed to high neonatal plasma prolactin, however, as values were the same whether infants were fed early maternal milk or mature donor breast milk.

It has been argued that hyperprolactinaemia, which even occurs in anencephalic neonates,[5 29] implies a failure of prolactin inhibition, by prolactin inhibitory factor, rather than a stimulation of release. Maturation of the ability to release prolactin inhibitory factor[5 11] could account in part for the progressive decline in plasma prolactin during the early months observed here and described previously. However, our data suggest a more complex explanation. Firstly, in the most immature infants, below 28 weeks' gestation, plasma values rose considerably over a period of weeks from the nadir at seven to eight days; such a *rise* is difficult to reconcile with the explanation of hyperprolactinaemia above. Furthermore, boys showed a much more rapid decline in values during the first two months than that seen in girls.

The sex difference in plasma prolactin in preterm infants, found also after adjustment for potentially confounding factors, was of interest. In adolescence and adulthood, females have higher prolactin values than males, principally early in the menstrual cycle when plasma oestrogen is high.[10] This sex difference has not been described during infancy or childhood. Indeed, in a much smaller sample it was preterm boys who transiently had higher plasma prolactin concentrations during the first week.[10] We found girls had transiently higher values after birth (consistent with a previous observation[15] based on cord blood analyses), and beyond 2 weeks of age when a major and progressive divergence in plasma prolactin between boys and girls was found. It requires exploration whether this difference could contribute to the well described poorer prognosis in boy preterm neonates.[30 31]

Maternal hypertension has been associated with an increase in plasma prolactin in cord blood.[21] It might be supposed that maternal pre-eclampsia had exerted a transient influence on the metabolic milieu of the fetus. However, our data show, surprisingly, that the association between high plasma prolactin and pregnancy related hypertension persists and increases in magnitude during the first two months (even after adjustment for confounding factors). The possibility is raised therefore that pregnancy related hypertensive disease might induce long term changes in the infant's endocrine state.

Diet was a major factor influencing plasma prolactin. In a strictly randomised comparison infants fed preterm formula developed lower plasma prolactin concentrations than those fed donor breast milk or standard formula (when these diets were used alone or as supplements to mothers' milk). The preterm formula was enriched in protein, energy, sodium, and other minerals. Ertl *et al* showed a significant postnatal decline in plasma prolactin,[32] as seen here in infants fed the preterm formula with sodium chloride supplementation. We found that plasma sodium and plasma prolactin were unrelated. While this does not exclude the possibility that our dietary effect was solely due to differences in salt intake, effects of other nutrients on prolactin release need to be excluded.

Prolactin has been identified as a possible trigger for surfactant synthesis.[12–17] Fetal prolactin secretion rises before surfactant production and there are prolactin receptors in the lung,[16] and after experimental administration of prolactin to fetal rabbits pulmonary lecithin content increases rapidly.[13] Some investigators find that a low plasma prolactin concentration in cord blood relates to the development of respiratory distress[6 7 12]; others do not[20 22] and claim low plasma prolactin is simply a marker for low gestation.[20] Such reports have relied on simple correlative analyses, however, with little adjustment for potentially confounding factors. Moreover, these investigations have related values at birth to the incidence of respiratory distress and have not examined the association between the subsequent development of low plasma prolactin and the persistence of respiratory disease. Our raw data showed a strong association between the incidence of respiratory disease and minimum plasma prolactin, with a sharp rise in incidence as prolactin values fell below 1000 mU/l (32·9 μg/l). After adjusting for confounding factors, this association was not sustained, casting doubt on some previous observations. Nevertheless, the subsequent development of low plasma prolactin was strongly and independently related to the duration of severe respiratory disease. This relationship held when minimum plasma prolactin was treated as a continuous variable, but data modelling showed that for prognostic purposes, a minimum value below 1000 mU/l (32·9 μg/l) was associated with a major increase in duration of mechanical ventilation. Infants whose plasma prolactin concentration fell below 1000 mU/l (32·9 μg/l) had a more than twofold increase in the number of days of ventilation that they required and were over twice as likely to be ventilated for more than seven days, even after adjusting for birth weight, gestation, fetal growth retardation, sex, pre-eclampsia, low Apgar scores, and other major factors.

After adjusting for the same factors, infants whose plasma prolactin fell below 1000 mU/l (32·9 μg/l) took 20% longer (median three days longer) to attain full enteral feeds and, more important, had a linear growth rate 30% lower than in infants in whom values remained above this concentration. Possibly, these outcomes related in part to slower gut maturation in those with low plasma prolactin.[23–26] It is unlikely that delayed establishment of enteral feeds and reduced linear growth in those with low plasma prolactin simply reflected increased respiratory disease in this group, as adjustment for the presence and duration of severe lung disease did not abolish these associations. Interestingly, low prolactin values only related to reduced linear growth and not reduced weight gain or head growth. Low plasma prolactin might have had a selective effect on nutrient absorption, with reduction in intestinal transport of bone mineral substrate.

This speculation accords with Mainoya's experimental findings in rats that prolactin enhanced jejunal absorption of calcium (and other ions).[26] Furthermore, prolactin has been implicated in regulation of 1–25 hydroxyvitamin D production,[33] and this might also influence bone growth. Indeed in humans with hypopituitarism prolactin treatment promotes skeletal growth.[3]

Preterm birth may disrupt normal endocrine development. Previously we have identified (in the same cohort) low plasma concentrations of two other hormones that may have an important bearing on clinical outcome: low neonatal triiodothyronine concentrations were associated with later reduced developmental scores[34] and low testosterone values in boys with failure of testicular descent.[35] In this study we have presented a further example of an early endocrine disturbance that relates to an adverse outcome: preterm infants, born before the normal rise in fetal prolactin in the third trimester, may have low plasma prolactin concentrations and these are strongly related to prolonged respiratory disease, delay in establishment of full enteral feeds, and reduced linear growth performance. Collectively, these data are relevant to the important question, requiring further scientific consideration, of whether infants of low gestation require multiple endocrine replacement treatment.

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Social integration of the older thalassaemic patient

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Abstract

Because social policy favours the fullest possible social integration of chronically ill patients, we have evaluated the facilities that are needed to achieve this for patients with β thalassaemia major in the light of the therapeutic advances that now permit them to survive into adulthood. We have investigated the social integration of adolescent and young adult thalassaemic patients, 171 from Greece and 112 from Ferrara in Italy. Patients in both areas show a good level of social integration and favourable self image, indicating what may be achieved by providing psychosocial support as part of a comprehensive approach to treatment.

β Thalassaemia is a chronic, genetically determined haematological disorder characterised by severe haemolytic anaemia as a result of deficient synthesis of β chains of the haemoglobin.[1 2] The anaemia demands frequent blood transfusions to maintain life, while haemosiderosis and other complications of the disease require a continuous and distressing treatment regimen that includes parenteral iron chelation treatment, regular medical supervision, frequent admission to hospital, and (on many occasions) operation. Until a few years ago thalassaemia was regarded as a uniformly fatal disease and death was expected to occur before adulthood. Recent developments, however, have introduced brighter prospects of survival given good compliance with the latest treatments.[3] Thalassaemia should no longer be seen exclusively as a disease of childhood, for patients now have the prospect of survival beyond adolescence in countries whose health services are able to supply adequate treatment.

To some extent the limiting factor in survival is the psychological element in compliance with the treatment protocol, which is related to coping with the many problems that we shall describe. The provision of psychosocial support for patients is therefore of primary importance and is an important topic of investigation. Continuity of support may be important too: in many places the structure of the health services requires that patients be transferred from paediatric to adult units at adolescence, a move which can have an adverse effect on the young patient who has formed a stable relationship with familiar medical staff.

As with every chronic disease, thalassaemia is liable to lead to difficult social and psychological problems.[4] These arise particularly from the hereditary nature of the disease, the likelihood of physical deformity (especially of facial appearance), and the demands of regular blood transfusion and painful, time consuming iron chelation treatment. The difficulties can only increase if the older thalassaemic patients are unable to adopt the normal roles of adults in society. The ability to find adequate employment—or any at all—may be affected by the need for frequent time off for transfusion and other treatment, a factor that may already have had an impact on the level of education achieved. The probability of marriage and parenthood may in the past have been reduced by the disease's association with retarded sexual development. A further possible complication, affecting both the health and social condition of the patient, is diabetes.

It is clear that there are formidable obstacles to the integration of the thalassaemic patient into normal life, even though the need for this is well understood.[4 5] Under these circumstances, it is important to gain an understanding of thalassaemic patients' present position in society and quality of life, to identify relevant social and psychological factors, and to establish what can be achieved by the provision of appropriate support facilities.

The operative word in this is 'support', as in many cases the old attitudes persist; the patient must be protected and normal expectations in respect of education, work, sexual development, and reproduction do not apply.

The present paper offers a comparative description of two preliminary studies of adolescent and adult thalassaemic patients, one conducted in Greece (C Politis, M Fisfis, C Richardson, *et al*. The social status of the thalassaemia patient in Greece. Presented at 2nd International Conference on thalassaemia and the haemoglobinopathies, Crete, 1987) and the other in Italy. Both the treatment units are long established specialist centres for the care of thalassaemic patients of all ages in areas where the disease is an important social problem, and both offer a degree of psychosocial support to their patients. The results show that it is possible to achieve social integration for most thalassaemic patients, they offer a basis for comparison with other areas where no or minimal support is available, and they point to contrasts between these two different areas of southern Europe.

Patients and methods

The studies were performed independently in the Red Cross Thalassaemia Unit in Athens, Greece, and the Microcytemia Centre in Ferrara,

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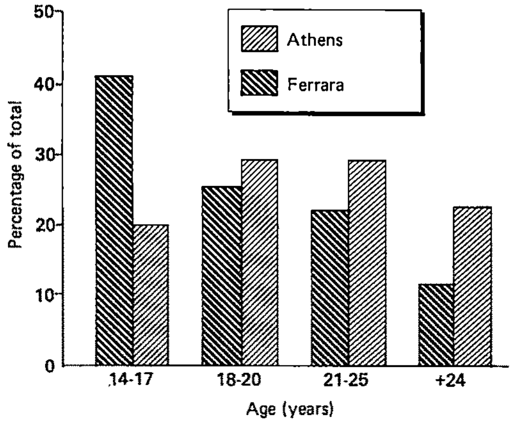
Italy. The Athens centre, established in 1955, cares for about 300 transfusion dependent thalassaemic patients drawn not only from the city but from all parts of southern Greece; the Ferrara unit, set up in 1972, treats about 170 patients from the immediate area of the city. Neither centre refers its patients elsewhere for treatment at adolescence. The centres follow similar policies of a multidisciplinary approach to the medical treatment and psychosocial support of their patients. Transfusion and other medical care is provided in two sessions a day in each centre. In Athens the therapeutic team comprises haematologists, paediatricians, specialised nurses, social workers, and psychologists, with a ratio of about one physician, two to three nurses, and one social worker to every 50 patients. The group in Ferrara comprises only paediatricians and nurses with a ratio of one physician to 42 patients, and one nurse to every 56 patients.

The sample sizes for the studies were 171 (88 male and 83 female patients) in Athens, and 112 (59 male and 53 female patients) in Ferrara; all patients were in the age range 14 to 34 years. The investigations were conducted by personal interview using questionnaires covering demographic data and items on topics relating to social integration including education, occupation, self image, and attitudes towards physical appearance. Both questionnaires consisted chiefly of precoded questions. Although the questionnaires were designed independently by the Greek and Italian medical groups (in collaboration with the Focus Social Research Centre, Athens, and the Sociology Department of the University of Messina, respectively), much basic information was covered by questions that were sufficiently similar to permit comparison between the two surveys. In addition to the information gathered by interview, the presence of diabetes was noted from the medical history.



Age distribution of patients in Athens (male:female ratio 51:49) and Ferrara (male:female ratio 53:47).

Results

The age distribution of patients is shown in the figure. Patients in Ferrara tended to be younger than those in Athens. Of those aged over 25 years, three of five male and five of eight female patients in Ferrara were married, compared with none of 22 male and two of 16 female patients in Athens. There were also three younger married patients in the Athens Red Cross group whereas there was no married thalassaemic patient in Ferrara under 25 years of age.

Thirty eight (22%) of the 171 Athens patients and four (4%) of the 112 Ferrara patients had only elementary education ($p<0{\cdot}0001$, χ^2 test), and 46 (34%) of the 136 patients aged over 18 years in Athens had received or were receiving university level education, compared with only four of 65 (6%) in Ferrara ($p<0{\cdot}0001$).

Data concerning occupation are presented in table 1. 'Housewives' in Athens were those who said that they were occupied with household duties, irrespective of marital state; in Ferrara, housewives were not recorded separately from the 'unemployed' category. A log linear model relating occupation (housewives were combined with 'unemployed' in Athens), sex, age, and place was found to require the inclusion of the interaction term between occupation and place ($\chi^2_2=12{\cdot}43$, $p=0{\cdot}002$); this means that the distribution of occupations was not the same in the two cities, even after controlling for sex and age differences. It is noticeable that in Athens there were more students and fewer unemployed than in Ferrara. The occupational distribution of the Greek patients did not differ from that of the Greek general population, whereas the Ferrara patients included both more students and more unemployed, and correspondingly fewer who were employed, than the Italian general population in the same age range (table 2).

Responses to an item concerning satisfaction with work were similar in the two cities; 30% of working patients in Athens and 31% in Ferrara said that they were satisfied with their work. In addition, patients in Athens currently receiving higher education were asked how satisfied they were with their studies, and 22% responded that they were satisfied.

Satisfaction with available ways of spending one's free time was investigated in Ferrara by means of a five point scale of agreement or disagreement, to which 81% of patients responded

Table 1 Patients' occupations by sex, age, and city. Values are expressed as a percentage of each group

Age (years) and city	Male patients				Female patients				
	Total No	Studying	Employed	Unemployed	Total No	Studying	Employed	Housewife	Unemployed
Athens:									
14–17	20	80	5	15	14	71	7	0	21
18–20	20	45	40	15	30	63	10	7	20
21–24	26	31	46	23	23	48	17	17	17
⩾25	21	10	81	10	16	6	50	38	6
Ferrara:									
14–17	21	62	29	10	25	80	8	Not recorded	44
18–20	18	33	17	50	9	11	44	Not recorded	44
21–24	15	7	47	47	10	10	50	Not recorded	40
⩾25	5	0	100	0	8	0	38	Not recorded	63

Table 2 Occupation of thalassaemic patients aged 15–24 years in comparison with that of general population of the same age. Values are expressed as percentages of each group

	Athens		*Ferrara*	
	*General population**	*Patients*	*General population*[6]	*Patients*
Employed	24	22	37	27
Studying	57	55	39	42
Unemployed	19	23	24	30

*Source: Focus Social Research Centre.

Table 3 Self image of patients in Ferrara. Values are expressed as percentages of each group

	Self	*Others*
Do you consider yourself/think that others consider you:		
A normal person	70	74
Sick but can handle own problems	24	23
Sick and cannot handle own problems	6	2

Table 4 Self image of patients in Athens. Values are expressed as percentages for each variable

	*Agree**	*Neutral*	*Disagree**
Don't like to be centre of attention	37	32	31
I give up easily	39	14	47
It's best to let others decide for you	19	18	63
If find it difficult to make friends	28	12	60
I don't attach much importance to my appearance	30	14	56

*Completely or partly.

that they were completely or quite satisfied. The nearest equivalent question in the Athens study referred to 'going out', and 71% of patients said that they were able to go out as often as they wished.

Self image was also examined by similar but not identical questions in the two studies. Patients in Ferrara were asked if they saw themselves as 'a normal person', 'ill but able to handle my own problems', or 'ill and unable to handle my own problems', and also asked how they thought that others saw them. The responses (table 3) did not depend on age and sex. Unemployed patients were less likely to regard themselves as normal, but the difference was not significant (p=0·1). In Athens patients were asked to rate agreement with five statements on a five point scale (table 4). Responses were recorded in three categories, and were found not to depend on age or sex, but unemployed patients were more likely to agree that they gave up too easily (χ^2=9·88, df 4, p=0·04).

Diabetes was present in 6% of the Athens sample, and was not significantly correlated with self image. In Ferrara, 16% of the sample had diabetes; 14% of patients who saw themselves as normal people, and 11% who thought they could handle their own problems, had diabetes compared with 33% of those with the poorest self image, but the difference was not significant.

Discussion

The data from the studies of adolescent and adult thalassaemic patients in Athens and Ferrara show that, even though this chronic disease places a heavy burden on the patient, it does not necessarily prevent normal psychosocial development. None the less, the facts that one in five Greek patients had received no more than elementary education (compared with 8% of the general population in the same age range), that only two of the Greek adult patients were married, that few patients in Ferrara had advanced to higher education, and that the percentage of Italian patients with jobs was substantially lower than that in the general population, indicate the kind of problems that may arise. Even so, more than a quarter of the Italian patients were employed. In Athens, the distribution of occupations already matched that of the general population at the time of the survey and subsequently even more of the sample have found jobs as a result of recent legislation favouring the chronically ill and other groups with special needs, within the frame work of governmental policy for social integration.

The effect of legislation is also evident in the high percentage of the Greek sample who were studying at university or had completed university education (34% of those aged over 18 years, compared with 22% in the general population aged 18–34 years). Thalassaemic patients in Greece are able to benefit from exemption from university entrance examinations; this compensates for the interference of the disease and the demands of treatment with the thalassaemic child's education, although the desirability of such special provisions is not universally accepted within the patients' and parents' associations.

The self image of patients in both groups seemed to be quite good. There was some indication that unemployed patients might have a poorer self image. If this result can be confirmed in further investigations, it will emphasise the importance of achieving social integration to aid the patient's wellbeing. It is the policy of the World Health Organisation to support the integration of chronically ill people into the community; in the case of thalassaemia, the improved prognosis as a result of therapeutic advances means that current concepts of what is needed must be re-evaluated. A combined medical and psychosocial approach demands not only the necessary managerial team but also a different attitude on the part of health authorities and even more of society. The data presented here suggest that such re-orientation can have a considerable impact.

The results described in this paper show what has been achieved in two centres staffed by comprehensive therapeutic teams who encourage the independence of the patients and their psychosocial integration to the fullest possible degree. Furthermore, both centres offer continuity of support to the patient as the potentially traumatic referral to other units at adolescence is avoided. We strongly believe that this strategy is the key to the successful integration of thalassaemic patients, and we suggest that this kind of management is generally appropriate for chronically ill people.

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[illegible]

The iris in Williams syndrome

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Abstract

Forty three children with Williams syndrome and 124 control subjects had their eyes photographed. The photographs were examined by three ophthalmologists and four geneticists of varying experience. A stellate pattern was noted more often in the irides of patients with Williams syndrome (51%) than in those of the control subjects (12%), and was more difficult to detect, or was absent, in heavily pigmented irides. We conclude that the stellate pattern is of diagnostic importance, particularly if the pattern is carefully defined and the clinician is experienced.

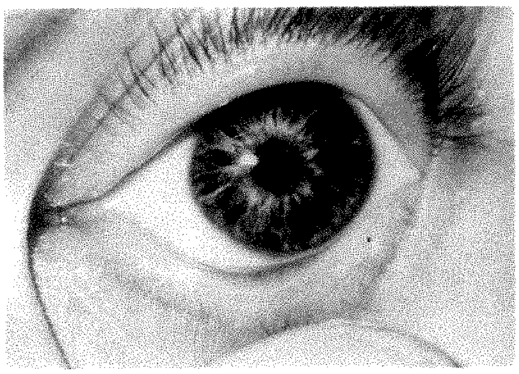

Figure 1 Stellate pattern of iris in a patient with Williams syndrome.

In 1961 Williams *et al* described a syndrome that included mental deficiency, characteristic elfin facies, and supravalvular aortic stenosis.[1] The same syndrome was also described by Beuren *et al* in 1962; they included peripheral pulmonary stenosis and dental anomalies among the features.[2] Further reports in 1963 noted the association with infantile hypercalcaemia and the phenotype has gradually been expanded.[3 4] Given the variability of the clinical picture the diagnosis can be difficult, and no single feature must always be present.

The most characteristic features of Williams syndrome are early feeding difficulties, mild growth retardation and mental deficiency, friendly and outgoing personality, hoarse voice, small widespaced teeth, and variable cardiovascular anomalies, usually including supravalvular aortic stenosis. The facies are characterised by malar flattening, full cheeks and lips with open mouth, long philtrum, depressed nasal bridge, short palpebral fissures, periorbital fullness, and epicanthic folds.[5]

Previous studies of ocular anomalies in Williams syndrome have described a characteristic pattern on the iris, strabismus, hypermetropia, and tortuousity of the retinal vessels.[6–9] The characteristic pattern (fig 1) has been described as 'stellate' or 'lacy and radial', and is thought to be caused by hypoplasia of the stroma of the iris.[10] A lateral displacement or absence of the anterior iris collarette has also been described.[9] Neither of these findings is pathognomonic for Williams syndrome and can be seen as normal variations in the general population, although the incidence of a stellate pattern in a normal population is unknown.

Most reports of Williams syndrome describe a stellate pattern of the iris as a characteristic sign. Incidences of 69%,[9] 74%,[6] and even 100% in a small group,[8] have been mentioned, and a high incidence of blue irides has also been reported—64%,[9] and 79%.[6] Williams noticed blue eyes in all four patients in his original report,[1] but did not mention any unusual pattern on the iris.

To find out if the iris has a characteristic colour in Williams syndrome patients the colour of irides in a normal population must be described. This was done in 1984 and 1986 by two groups of authors who examined 690 and 70 subjects, respectively; 55% were thought to have light irides and 45% dark irides.[11 12]

The intention of this study was to find out if a stellate pattern on the iris is a useful diagnostic marker in patients with Williams syndrome compared with a control group. We also wanted to compare the colours of irides of patients with Williams syndrome with those of the controls to see if we could correlate the stellate pattern with the colour of the irides.

Patients and methods

Through the parents' association of the Infantile Hypercalcaemia Foundation (Williams syndrome) we met 37 families with their children at their annual summer picnic in Hyde Park, London. We photographed each of their eyes separately. Another six children with Williams syndrome were photographed in our hospital, and so we obtained useful slides of 80 eyes. As a control group we took photographs of 124 children attending different clinics in the hospital, and of these 240 slides were useful.

All photographs were taken in the same way and by the same photographer (GA). A Nikon FM2 camera, with a Micro Nikkor 105 mm lens and a PN 11 extention ring, was used and gave a magnification on the film of 1:1. We used an Ektachrome 100 daylight balanced film and a portable, electronic Metz CT – 32 flash. For the photographs taken in Hyde Park we used a

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Table 1 Percentage of eyes showing stellate pattern in patients with Williams syndrome and in control subjects judged by seven observers

Observer	*Stellate pattern in patients with Williams syndrome*	*Stellate pattern in control subjects*	*p Value*	*Unable to tell*
1	64	1	<0·001	3
2	24	16	>0·05	14
3	28	6	<0·001	4
4	61	8	<0·001	15
5	59	25	<0·001	9
6	43	13	<0·001	15
7	80	16	<0·001	6
Mean (range)	51 (24–80)	12 (1–25)	<0·001	10 (3–15)

Table 2 Mean (range) percentage of eyes showing stellate pattern in patients with Williams syndrome and in control subjects as judged by experienced and less experienced observers

	Experienced observers (Nos 1 and 7)	*Less experienced observers (Nos 2–6)*
Stellate pattern in patients with Williams syndrome	72 (64–80)*	43 (24–61)**
Stellate pattern in control subjects	9 (1–16)*	14 (6–25)**
Unable to tell	5 (3–6)	11 (4–15)

*p<0·001; **p<0·001.

Table 3 Colour of irises in 43 patients with Williams syndrome and 124 control subjects

Colour group	*Mean value of observers as percentage of patients with Williams syndrome*	*Mean value of observers as percentage of control subjects*
1 (light blue)	12	23
2 (darker blue)	38	28
3 (green)	33	20
4 (light brown)	8	21
5 (dark brown)	9	8

black umbrella to exclude superfluous daylight. The power of the flash is such that any ambient light is completely negated, ensuring that the indoor and outdoor photographs are comparable.

The 320 slides were mixed and were shown in random order to seven observers, three ophthalmologists and four geneticists. The observers were asked to say 'yes' if they noticed a stellate pattern, 'no' if they did not, and 'do not know' if they were unable to give an answer. They were also asked to score the colour of the irides with the help of a five number scale: 1=light blue, 2=darker blue, 3=green, 4=light brown, and 5=dark brown.

Results

The results of the study are seen in table 1. The mean incidence of stellate patterns of the irides in patients with Williams syndrome was 51% (range 24–80) among the seven observers. The mean incidence of stellate patterns among the control subjects was 12% (range 1–25). The incidence of irides in which the observers were unable to tell varied between 3% and 15%, with a mean value of 10%. A χ^2 analysis was done to see if there were significantly more stellate patterns in the patients than in the control subjects. The results were significant ($p<0·001$) for all but one of the observers. There was a difference between 'experienced' and less experienced observers. The experienced clinicians found stellate patterns in 72% (range 64–80) of patients with Williams syndrome and in 9% (range 1–16) of the control subjects. The results for the less experienced were 43% (range 24–61) and 14% (range 6–25%), respectively (table 2).

We found great discrepancies among the observers concerning the colour scoring. The mean values among all the observers are shown in table 3. Of the patients with Williams syndrome, 50% were found to have blue irides (colour group 1 and 2) compared with 51% of those of the controls (table 3).

Discussion

There are problems in comparing the incidence of stellate patterns on the irides in patients with Williams syndrome in different studies as a definition of the pattern is difficult, and there are even greater problems in comparing the colour of the irides as objective definitions of the different colours vary from study to study. We did not find any significant differences in colour of the irides between patients and control subjects. There were, however, considerable problems with interobserver differences. It was also noted that the detection of a stellate iris pattern was much more difficult in dark irides than in light ones. Figure 1 shows a 'typical' stellate pattern on the iris of a patient with Williams syndrome. In fig 2, however, the features of the pattern are less obvious and thus more difficult for the observers to score.

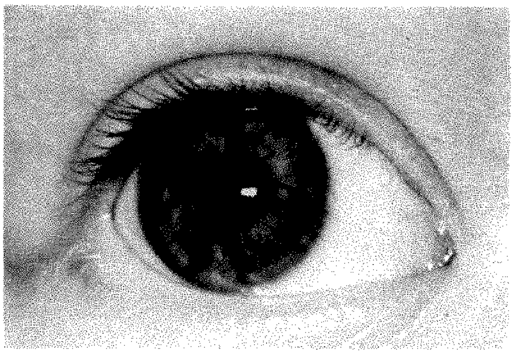

Figure 2 Iris of a patient with Williams syndrome in which features of the stellate pattern are less obvious.

The patterns on the irides in patients with Williams syndrome are described as stroma hypoplasia,[10] abnormality anterior to the iris,[6] and lateral displacement or absence of the iris collarette.[9] We believe that the irides in this syndrome are characterised by a normal pigmentary frill and a normal pupillary portion central to the collarette. There is variable peripheral displacement of the collarette, often giving it a sinous appearance, and peripheral to the collarette there are raised trabeculas anterior to the usual stroma of the iris. These trabeculas seem to be more radial than in normal irides and there are prominent crossings of the trabeculas. The far periphery of the iris seems normal.

We conclude that Williams syndrome does have a characteristic iris pattern that can be described as stellate, and which occurs in at least half of the patients. We believe that the stellate pattern is a sign of diagnostic importance provided that care is taken to define the features of the pattern accurately. Finally, increased clinical experience seems to make the stellate pattern of the iris a more useful tool in discriminating patients with Williams syndrome from a group of control subjects.

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Perforated duodenal ulcer: an unusual complication of gastroenteritis

Jane M Wilson, Christopher R Darby

Abstract

A 7 year old boy was admitted to hospital with gastroenteritis, which was complicated by an acute perforated duodenal ulcer. After oversewing of the perforation he made an uncomplicated recovery. Peptic ulceration is underdiagnosed in childhood and this leads to delay in diagnosis and appropriate management. Ulceration is associated with severe illness and viral infections, but perforation is rare.

As long ago as 1941 it was suggested that acute peptic ulceration in childhood was not rare, but that it was overlooked. Despite this, it does not feature prominently in the textbooks, where it is said to be an uncommon but well recognised complication of many serious diseases or severe stress in childhood.[1] Children usually present with vomiting or gastrointestinal haemorrhage, or both,[2] or the ulcer may be an accidental finding at necropsy.[3] Perforation is rare.[2 3] We report perforation of an acute duodenal ulcer in a child who was not seriously ill but who was admitted with gastroenteritis.

Case report

A 7 year old retarded boy was admitted by his general practitioner with a 48 hour history of diarrhoea and vomiting. He had just spent the weekend at a children's respite home where most of the staff and residents had been struck down by similar symptoms. He was taking no drugs.

He had a history of birth asphyxia and delayed milestones, he had been unable to sit by the age of 8 months, and had generalised hypotonia at the age of 1 year. A translocation of chromosomes 1 and 4 was diagnosed, and this was thought to have contributed to his handicap. At the time of his presentation he was walking well, but was mentally retarded with considerable behavioural problems.

His maternal grandfather had had a duodenal ulcer diagnosed at endoscopy, and his maternal great grandfather was also said to have had an ulcer.

At presentation the boy was lethargic, miserable, and extremely dehydrated, though still passing urine. His abdomen was soft. Simple infective gastroenteritis was diagnosed, and he was admitted for oral rehydration.

Overnight the diarrhoea and vomiting subsided and he took oral fluids. By 18 hours after admission he was well hydrated and normal food was reintroduced. An hour later the vomiting recommenced and he had a large haematemesis and collapsed, becoming grey, cold, and clammy with unrecordable blood pressure and a heart rate of 170 beats/minute. His abdomen remained soft, but had become mildly distended. On rectal examination the faeces were soft and of normal colour.

After he had been resuscitated a chest radiograph was taken, which showed air under the diaphragm. At operation his abdomen was hugely distended, and a midline incision released a large amount of free gas; 1400 ml of bile stained fluid contaminated with food were also released. The stomach and duodenum were exposed and a perforated acute duodenal ulcer 1 cm in diameter was found. After copious lavage the perforation and abdomen were closed and the patient made an uneventful recovery. Subsequent estimation of the serum gastrin concentration was normal.

Discussion

Peptic ulceration in children is not new: in 1826 a perforated gastric ulcer was reported in a 2 day old child.[4] It has, however, been suggested that peptic ulceration is still underdiagnosed, and there are many uncertainties about its natural history.[4]

Peptic ulceration is rarely diagnosed in children, causing only between 3·4/10 000, and 1/4700 admissions.[5 3] At the Hospital for Sick Children, Toronto, only six perforations were detected in 20 years,[3] at Montreal Children's Hospital eight in 11 years,[2] and at the Children's Hospital, Pittsburgh, 11 in 20 years.

Childhood peptic ulcers are either 'primary' or 'secondary'. Primary ulcers present at a mean age of 8 years, the male:female ratio is 4:1,[3] there is often a strong family history, and they occur most commonly in patients with blood group O.[5] Secondary ulcers are precipitated by severe burns (Curling's ulcer), raised intracranial pressure (Cushing's ulcer), and other severe illnesses—for example, shock, sepsis, or cancer. In infants 80% of ulcers are secondary, but in older age groups the incidence drops to 20%.[1]

A recent study of 31 infants and children in whom acute duodenal ulceration had been diagnosed endoscopically showed that 29 (94%) had a preceding illness: diarrhoea, respiratory infection, or fever. None of the ulcers had perforated. Evidence collected from that study suggested that acute duodenal ulceration can develop after viral illness, but heals quickly irrespective of the site and the number of ulcers.[6]

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An unusual cause of thoracic mass

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Abstract

A previously well 10 year old boy presented with scoliosis, a mass in the chest wall, and a pleural effusion. Chest radiography showed the triad of chronic consolidation, pleural effusion, and rib periostitis. Investigations confirmed thoracic actinomycosis. Tissue spread was evaluated by computed tomography. It was successfully treated with benzylpenicillin, which was later replaced by clindamycin.

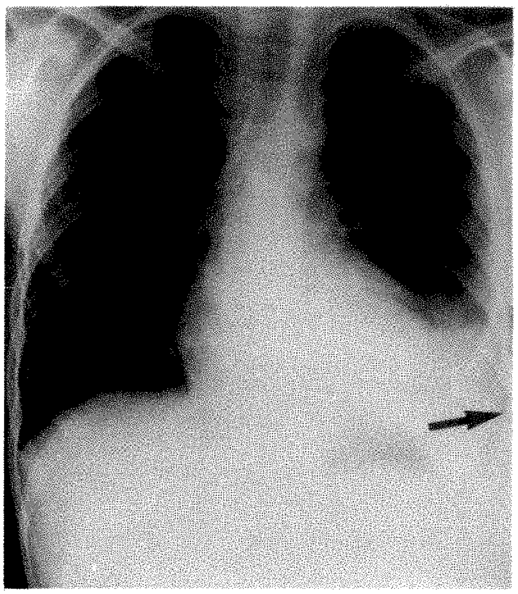
Thoracic actinomycosis is extremely rare in children, especially if they are immunocompetent, and is not often considered in the differential diagnosis of paediatric pulmonary disease. This case illustrates the typical presentation, classic radiological and microbiological findings, and treatment of this subacute infection.

Case report

A 10 year old boy presented with lethargy, weight loss, and chest pain. A submandibular swelling and a mass in the chest wall had been noted recently. He had no history of anorexia, sweats, cough, fever, or sputum, but had mild asthma; he had not been in contact with tuberculosis.

He looked ill, but had no fever, lymphadenopathy, or rash. His weight was on the tenth centile. He had dental caries and diffuse swelling of the left submandibular area. There was a central abscess within a large, indurated, tender swelling of his left lower anterior chest wall. He had thoracic scoliosis, diminished expansion, dullness to percussion, and a patch of bronchial breathing with scattered crepitations at the left base. Liver and spleen were not enlarged.

Results of investigations included haemoglobin concentration 99 g/l, white cell count $16{\cdot}3\times10^9$/l, neutrophil count $13{\cdot}7\times10^9$/l, erythrocyte sedimentation rate 42 mm in the first hour, and C reactive protein concentration 73 mg/l (reference range <6). A chest radiograph showed thickening of the left chest wall, consolidation of the left lower lobe, left pleural effusion, and periostitis of the left seventh and eighth ribs (figure). A computed tomogram of the thorax showed a lesion spreading from the left lower lobe of the lung to the pleura, invading the ribs, and then passing through the chest wall. Radiographs of the mandible, abdominal ultrasound scan, liver function tests, and immunological screen were normal. Blood cultures grew no pathogens and a Mantoux test was negative.



Chest radiograph showing triad of chronic consolidation, pleural effusion, and rib periostitis (arrowed).

When the abscess pointed, it was incised. Examination of the pus showed sulphur granules and Gram positive branching filaments with clubs; *Actinomyces israelii* was grown. High doses of benzylpenicillin were given intravenously, and four carious teeth extracted. After two weeks the erythrocyte sedimentation rate was 14 mm/in the first hour and C reactive protein concentration 7 mg/l. One week later, as he had developed urticaria, clindamycin was substituted for benzylpenicillin. After five weeks of parenteral treatment, he was discharged taking clindamycin orally. This was continued for eight months and during this time his weight increased and the chest signs resolved. A

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further chest radiograph showed only a small residual pleural effusion.

Discussion

Invasive actinomycosis affects the cervicofacial region in 65% of cases, the abdomen in 20% of cases, and the thorax in only 15% of cases. Thoracic actinomycosis is rare in childhood; we could find only two reports of its occurrence in the United Kingdom.[1 2] Lack of familiarity with the disease by both clinicians and radiologists may, however, lead to diagnostic error.

Actinomyces is a normal commensal of the human mouth. Pulmonary actinomycosis may result from infection from several sources—aspiration from the oral cavity, carriage into the lung on a foreign body, haematogenous seeding, or spread of existing cervicofacial or abdominal infection through the tissue planes.[3] Actinomyces are Gram positive, non-acid fast bacilli, and are facultative anaerobes. They are true bacteria, although they were previously classified with fungi because of their mycelial appearance and indolent clinical course. *A israelii* is the most common species, although there are others such as *Actinomyces meyerii* that can cause similar disease.

The clinical features in this case are characteristic of actinomycosis. Actinomyces infections do not respect tissue planes; the complex of pulmonary, pleural, and chest wall disease is unusual with other infections.[4] Actinomycosis is rare in normal children, because dental caries or peridontitis are usually followed by rapid loss of the teeth.[5] It is more common in immunocompromised children, or among mentally subnormal children in institutions,[2] where poor dentition is common.

Diagnosis is often delayed because of failure to consider actinomycosis, and the difficulty in obtaining specimens and culturing them anaerobically. Examination of pus may show sulphur granules, which are suggestive but not diagnostic of actinomycosis. Microscopic examination shows Gram positive branching filaments with terminal clubs, but often the organism is not seen after anaerobic culture. Recovery of the organism from sputum means nothing, as it is a normal oral commensal. The classic radiological presentation of thoracic actinomycosis is the triad of chronic consolidation, pleural effusion, and overlying rib periostitis as was seen in this case.[2] Periostitis indicates chronic infection, rather than destruction by acute infection or malignancy. Computed tomography is useful in evaluating the lesion.[6] The differential diagnosis is wide, and includes tuberculosis, lung abscess, carcinoma, reticulosis, and atypical pneumonia.[3 5]

The use of antibiotics in the treatment of actinomycosis has resulted in a high rate of cure, even in advanced disease, and the most appropriate drug is penicillin.[3] There is no agreement, however, about dosage or duration of treatment. Parenteral penicillin is usually given for several weeks, followed by penicillin orally for three to six months. In some centres high doses of oral penicillin alone have been used.[4] Other antibiotics have also been used successfully, including erythromycin, chloramphenicol, clindamycin, and lincomycin, particularly in cases of allergy to penicillin.

Prognosis is excellent when diagnosis has been reached and specific antibiotics used. Mortality in the past was related to late diagnosis, haematogenous spread, and injudicious surgical intervention.

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Spontaneous resolution of congenital nephrotic syndrome in a neonate

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Abstract

An infant with congenital nephrotic syndrome recovered spontaneously and completely by the age of 11 days and had remained well at the age of 1 year. This reinforces the view that reversible congenital nephrotic syndrome does occur and that it is not a single disease with a universally dismal prognosis.

Congenital nephrotic syndrome presents in the first three months of life,[1 2] and usually results in death in early childhood unless intensive treatment including renal transplantation is undertaken.[1–3]

Only four cases of congenital nephrotic syndrome with spontaneous recovery have previously been reported, and of these two did so at 10 and 25 months.[1 3] The other two were siblings whose mother had focal segmental glomerulosclerosis and were presumed to have been affected by humoral factors; they recovered in less than three weeks.[4]

Case report

A girl presented at the age of 92 hours with peripheral oedema. She was the first child of a 29 year old white mother; the pregnancy had been uncomplicated, with normal blood pressure, no proteinuria, and she had taken no medication. Family history was unremarkable. She was born at 38 weeks' gestation weighing 2466 g, and the 1 minute Apgar score was 9. The placenta weighed 640 g and was healthy.

Examination at 12 and 48 hours (because of poor feeding) showed no abnormality. By 92 hours she had only lost 16 g despite feeding poorly and she had developed oedema of the limbs and around the eyes. Her pulse was 160/min, respiratory rate 40/min, and blood pressure 75/49 mm Hg.

The urine looked clear, but there was gross haematuria and proteinuria on ward testing. There were no casts present. Urinary electrophoresis showed a heavy unselective proteinuria. The plasma protein concentrations were low; total protein was 30 g/l (albumin 20 g/l and globulin 10 g/l), confirming the diagnosis of nephrotic syndrome. Investigations did not reveal a cause for the congenital nephrotic syndrome; antenatal Veneral Disease Research Laboratory screening for syphilis was negative as were the baby's toxoplasma, rubella, herpes and cytomegalovirus titres. She had a normal female karyotype. Ultrasound scanning showed slight bilateral renal enlargement (kidney length 5·5 cm) with poor corticomedullary differentiation and no evidence of hydronephrosis or renal vein thrombosis. Her mother's urinary albumin:creatinine concentration ratio was normal at 1·9 mg/mmol (upper limit of reference range 3·5).

Over the next two days the baby's feeding improved, but she developed increasing oedema, gained 500 g in weight, and showed clinical signs of intravascular hypovolaemia with strikingly cold peripheries. Biochemical and haematological indices were consistent with hypovolaemia. Her plasma creatinine concentration was normal at 38 μmol/l, and the sodium was low at 126 mmol/l. Her urinary sodium was less than 5 mmol/l, and the urine: plasma ratio for urea was greater than 12 giving a value for fractional reabsorption of sodium of at least 99·6%. The haemoglobin concentration was 190 g/l.

She was treated with 15 ml/kg of plasma protein fraction and 2 mg frusemide given intravenously, which resulted in improved peripheral perfusion, a diuresis, and loss of 170 g in weight, a fall in haemoglobin concentration to 170 g/l, and correction of her plasma sodium concentration to 144 mmol/l.

Her proteinuria remained (maximal colour on test strip) for three days, then reduced gradually; by day 11 her urine contained no protein, her plasma albumin concentration had risen to 31 g/l, her oedema had completely resolved, and she was feeding well and gaining weight. A repeat ultrasound scan at 19 days showed kidneys of normal length (4·4 cm) with corticomedullary differentiation. At 1 month a dimercaptosuccinic acid scan was normal. At 1 year she remained completely well, with a urinary microalbumin concentration below the detection limit of the assay (12 mg/l).

Discussion

As this baby had proteinuria, hypoproteinaemia, and oedema at 4 days of age, she had by definition got congenital nephrotic syndrome. Renal biopsy was not carried out because of her spontaneous recovery, and no predisposing cause was identified. Only four cases have previously been described in which spontaneous resolution of congenital nephrotic syndrome occurred; in two this was after much longer (10 and 25 months),[1 3] and in one of these hypotensive treatment was required initially.[3] The other two cases were siblings whose mother had focal segmental glomerulosclerosis[4]; the index case's mother had normal urinary protein excretion. All other cases of congenital nephrotic syndrome that have resolved have required treatment with steroids,[5] or have been infants with congenital syphilis who have been treated with penicillin.

Congenital nephrotic syndrome is associated with various histological patterns, of which the Finnish type is most common. Others include diffuse mesangial sclerosis, focal segmental glomerulosclerosis, and—rarely—a pattern of minimal change seen in infants that have responded to treatment with steroids.[2] As congenital nephrotic syndrome is usually an irreversible debilitating condition that leads to death unless active treatment is instituted, it is likely that these rare cases that undergo spontaneous remission represent a separate histological subgroup. To our knowledge this girl had the earliest spontaneous recovery yet described. Her case reinforces the view that reversible congenital nephrotic syndrome does occur, and that congenital nephrotic syndrome is not a single disease with a universally dismal prognosis.

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Congenital diaphragmatic hernia: impact of prostanoids in the perioperative period

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Abstract

A prospective study of 10 neonates with congenital diaphragmatic hernia and five controls to determine the importance of prostanoid concentrations perioperatively and the relation with persistent pulmonary hypertension (PPH) is reported. In neonates with congenital diaphragmatic hernia postoperative concentrations of the vasoconstrictor thromboxane B_2 rose significantly and were higher during episodes of PPH; this rise may provoke PPH and subsequent right to left shunting.

The outcome in patients with congenital diaphragmatic hernia depends either on the gravity of pulmonary hypoplasia or on the combination of pulmonary hypoplasia with persistent pulmonary hypertension (PPH).[1]

Degradation products of arachidonic acid such as the leukotrienes[2] and the prostaglandins and thromboxanes (the so called prostanoids) have been associated with the generation of PPH in neonates.[3]

The purpose of this prospective study was to determine the importance of prostanoid concentrations and ventilatory variables in patients with congenital diaphragmatic hernia with and without PPH in the perioperative period.

Patients and methods

During the study period, December 1987 to February 1989, 10 consecutive neonates with congenital diaphragmatic hernia (mean gestational age 37·6 weeks, birth weight 3050 g) were admitted to the paediatric surgical intensive care unit, because of severe respiratory insufficiency within six hours after birth.

During the same study period five patients with oesophageal atresia (mean gestational age 36 weeks, birth weight 2645 g) served as a control group and they followed the same protocol.

Registration of ventilatory variables was carried out on admission, one hour before surgery, and one and six hours after surgery. These variables included the alveolar arterial oxygen differences ($AaDO_2$), mean airway pressure, oxygenation index, and ventilation index.[4]

Determination of thromboxane B_2, a stable metabolite of the vasocontrictor thromboxane A_2, and 6-keto-prostaglandin $F_{1\alpha}$ (PgF), a stable metabolite of the vasodilator prostacycline, were analysed by radioimmunoassay.

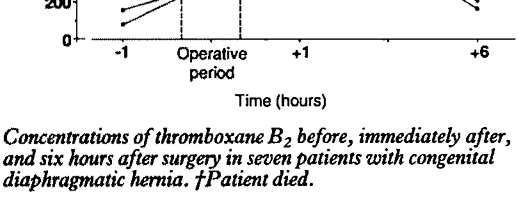
The diagnosis of PPH was confirmed with the following diagnostic procedures: (i) hyperoxic hyperventilation test in which the arterial oxygen pressure (PaO_2) increased to >13·3 kPa after hyperventilation with 100% oxygen; (ii) preductal and postductal PaO_2 differential of >2·7 kPa considered evidence of a transductal shunt; and (iii) positive contrast echocardiography showing right to left shunting.[5]

As the distributions of most variables were highly skewed the median and range were used as descriptive statistics in the statistical analysis.

Results

Ten patients with congenital diaphragmatic hernia and five controls were examined. Two of the patients had a right sided defect and eight had a left sided defect, two had never had surgery because their condition deteriorated rapidly. These two patients died at 15 and 25 hours after admission and necropsy confirmed severe lung hypoplasia. A third patient did not undergo surgery because he had an isoelectric electroencephalogram after a prolonged period of hypoxia immediately after birth. One of the seven patients who underwent surgery had trisomy 18 and died. All five control patients were operated on. One prematurely born infant died after severe intracranial haemorrhage.

In patients with congenital diaphragmatic hernia median concentration of thromboxane B_2 rose significantly from 250 (range 81–703) pmol/ml preoperatively to 740 (range 443–1030) pmol/ml postoperatively (signed rank test, p=0·018). In the control group concentrations of thromboxane B_2 were 376 (range 250–497) pmol/ml preoperatively and 185 (range 50–1010) pmol/ml postoperatively (p=0·7). Plasma concentrations of PgF, increased from 260 (range 140–8835) to 2460 (range 1709–4150) pmol/ml in patients with congenital diaphragmatic hernia and from 455 (range 30–986) to 1145 (range 180–3682) pmol/ml in control patients; this was not significant. The increased concentrations of



Concentrations of thromboxane B_2 before, immediately after, and six hours after surgery in seven patients with congenital diaphragmatic hernia. †Patient died.

Median (range) ventilatory variables and prostanoid concentrations in patients with congenital diaphragmatic hernia with and without PPH

	Congenital diaphragmatic hernia without PPH	*Congenital diaphragmatic hernia with PPH*	*p Value*
AaDO$_2$	201 (127–385)	559 (318–623)	0·016
Mean airway pressure	11 (6–13)	9 (8–15)	0·9
Oxygenation index	4 (2–10)	21 (8–30)	0·016
Ventilation index	630 (330–1296)	542 (497–1138)	0·8
Thromboxane B$_2$ (pmol/ml)	312 (262–656)	774 (477–3699)	0·03
PgF (pmol/ml)	726 (562–1056)	938 (55–2713)	0·3

thromboxane B_2 at one hour postoperatively dropped to preoperative concentrations in all but two patients with congenital diaphragmatic hernia (figure). One of these patients died with high concentrations and the clinical picture of PPH.

In five patients with congenital diaphragmatic hernia at least one episode of PPH was diagnosed. The average values of the ventilatory variables and prostanoid concentrations are presented in the table, and compared with the values in patients without episodes of PPH. In patients with right to left shunting AaDO$_2$, oxygenation index, and thromboxane B_2 concentrations were significantly higher than in those without right to left shunting.

Discussion

Oxygenation of neonates with congenital diaphragmatic hernia in the perioperative period remains a challenging problem because of the combination of pulmonary hypoplasia and PPH.

Recently Hammerman and coworkers correlated the presence of PPH in neonates to increased concentrations of thromboxane B_2.[3] The pulmonary vascular system of the patient with congenital diaphragmatic hernia differs from that of normal newborns and may overreact to different stimuli.[6]

In patients with congenital diaphragmatic hernia plasma concentrations of the vasoconstrictive metabolite thromboxane B_2 increased significantly during the surgical and anaesthetic procedure. If the pulmonary vascular system is still susceptible to vasoconstriction, it is obvious that in these cases pulmonary artery pressure may rise and right to left shunting may occur. In five out of seven patients thromboxane B_2 concentrations turned to baseline values at six hours postoperatively, showing that the rise of thromboxane B_2 is related to the operation. In other words, the surgical procedure may provoke PPH in a 'susceptible' pulmonary vascular system.

Ventilatory variables have proved their use in prediction of survival in patients with congenital diaphragmatic hernia.[1] The AaDO$_2$ and the oxygenation index values are significantly higher in patients who have PPH. In these patients, concentrations of thromboxane B_2 have increased and might reflect an imbalance between vasodilation and vasoconstriction, dipping to vasoconstriction.

In conclusion: we have shown that during surgery there is activation of the arachidonic prostanoid cascade leading to a rise in thromboxane B_2 concentrations in patients with congenital diaphragmatic hernia. This may be an additional risk factor for right to left shunting postoperatively and it may be an argument for delayed surgery till the moment when the pulmonary vascular system has become 'stable'.

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CURRENT TOPIC

Reflux vomiting

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It is generally accepted that vomiting may occur by regurgitation of stomach contents as a result of gastro-oesophageal reflux or by evoking the emetic reflex causing contraction of the diaphragm, intercostal and anterior abdominal muscles, and forcible expulsions of gastric contents. Regurgitation of feeds because of gastro-oesophageal reflux is common in the young infant and in most, is little more than an inconvenience, with the affected infant healthy and thriving. In a few, however, regurgitation is symptomatic and is an important clinical problem resulting in failure to thrive, haematemesis, iron deficiency anaemia, oesophagitis, stricture formation, apnoea, obstructive airways disease, and aspiration pneumonia. In an important study Carré showed that 60% of infants who regurgitated stopped by 18 months of age with most symptoms settling by the age of 9 months.[1] Thirty percent of the infants he studied continued to have symptoms until at least 4 years of age and 10% developed one or more of the above complications. The prevalence of gastro-oesophageal reflux, and the frequency of the above complications is, however, difficult to ascertain as most infants who regurgitate do not come to medical attention and in nearly all, spontaneous resolution of their symptoms occurs. In a further study by Carré he suggested that one in 500 infants who attended a paediatric outpatient clinic had gastro-oesophageal reflux.[2] While the prevalence and incidence of complications of gastro-oesophageal reflux in infants might not be clear, a consideration of the anatomy and physiology of the motor activity of the oesophagus and stomach provides a framework within which the nature of reflux vomiting can be understood.

The anatomy and physiology of the oesophagus and lower oesophageal sphincter

The anatomy of the oesophagus is different to any other part of the gastrointestinal tract. The mucosa is composed of stratified squamous epithelium that is not resistant to gastric acid. The muscularis propria of the upper third is composed of striated muscle and it is only in the lower third that there is smooth muscle arranged into an outer longitudinal and inner circular layer with a nerve plexus between them. At the lower end of the oesophagus the muscle layer is modified into an area resistant to stretch, the lower oesophageal sphincter, which exhibits tonic high pressure. A number of features account for this activity. The smooth muscle of the high pressure zone is different from that of the body of the oesophagus in terms of its compliance[3] and sensitivity to polypeptide hormones.[4] The length of the intra-abdominal segment of the oesophagus, the gastro-oesophageal angle, diaphragmatic crura, and mucosal flap valve, all form important accessory features for the maintenance of the effective function of the lower oesophageal sphincter.[5 6]

Boluses of food are propelled to the stomach in 5–15 seconds by a series of events resulting in contraction of pharyngeal muscles, peristalsis of the body of the oesophagus and relaxation of the lower oesophageal sphincter. These events are controlled by two major elements. The brain stem, particularly the ninth, 10th, and 12th nerve nuclei control contraction of the striated muscle of the mouth, pharynx, and upper oesophagus, and the smooth muscle of the remainder of the body of the oesophagus. The nature of the lower oesophageal sphincter itself is important in maintaining the high pressure zone in addition to the effects of intrinsic and extrinsic innervation. In addition to the lower oesophageal sphincter relaxing in response to swallowing, the proximal stomach also relaxes to accommodate the ingested food. Coordinated contraction of the gastric antrum, pylorus, and duodenum results in the stomach emptying the ingested food into the small intestine.

Mechanisms of gastro-oesophageal reflux

Gastro-oesophageal reflux may occur because of a variety of defects of function and structure of the components described above. A difference in pressure between the stomach and oesophagus is clearly important as is failure of the mechanisms present that prevent the flow of gastric contents down such a pressure gradient. Recent studies suggest that a fall in lower oesophageal sphincter pressure to 0·4 kPa (3 mm Hg) or less must occur for gastric contents to be refluxed into the oesophagus.[7]

Episodes of reflux are associated with three groups of disorder of the lower oesophageal sphincter: (i) a low basal sphincter pressure, (ii) inappropriate sphincter relaxation, which is either synchronous or asynchronous with swallowing, or (iii) transient increases in intra-abdominal or gastric pressure alone or in combination with any of the above. In most normal individuals some gastro-oesophageal reflux occurs postprandially due to rises in intragastric pressure with reflux occurring when there is complete relaxation of the lower oesophageal sphincter as occurs with swallowing. Such refluxed material in the normal individual is rapidly cleared from the oesophagus by secondary peristalsis.

In children with symptomatic gastro-oesophageal reflux most reflux episodes are due to transient relaxation of the lower oesophageal sphincter, which is asynchronous with swallowing.[8 9] However, in those that do not have symptomatic or complicated gastro-oesophageal reflux—that is, those who are healthy, thriving infants who usually regurgitate postprandially—the mechanism is different. In such infants reflux occurs most usually synchronously with swallowing but the lower oesophageal sphincter relaxation occurs for a longer period of time than in infants who do not have lower gastro-oesophageal reflux.[9] Thus it would seem that their reflux is an exaggeration of the physiological reflux that occurs in normal individuals during and after eating. Low basal lower oesophageal sphincter pressures are an unusual association with gastro-oesophageal reflux and in two studies were only found in those with severe oesophagitis or neurological disorders.[8 9] Thus the idea of a 'lax cardio-oesophageal sphincter' commonly being responsible for gastro-oesophageal reflux is not borne out by scientific study.

Whether oesophagitis occurs is dependent on the ability of the infant to clear the oesophagus of refluxed gastric acid. In infants who only 'spit up', peristalsis of the oesophageal body is the same as in control infants and refluxed acid is cleared promptly. In those who have symptomatic gastro-oesophageal reflux and transient inappropriate or asynchronous lower oesophageal sphincter relaxation the amplitude of both primary and secondary peristalic waves are reduced and acid clearance times prolonged.[9] These findings are most pronounced in infants with severe oesophagitis where in addition, low amplitude bizarre multipeaked waveforms are seen, which are reminiscent of those occurring in neuropathic forms of intestinal pseudo-obstruction. Measurement of oesophageal transit shows that delayed oesophageal acid clearance in patients with oesophagitis is due to a disorder of oesophageal propulsion.[10] In simultaneous motility-barium clearance studies low amplitude and bizarre peristaltic waves result in retrograde flux of barium back through the advancing peristaltic contraction.[11] The retrograde flow causes incomplete clearance of the barium. Whether the disturbed motor activity is simply as a consequence of the smooth muscle and oesophageal innervation operating in the environment of the inflammatory response to the prolonged acid exposure or whether it is caused by an underlying disorder of the motor control mechanisms is not entirely clear but at least two studies in adults suggest the latter.[11 12]

It seems clear that mechanisms of gastro-oesophageal reflux involve the interplay of oesophageal motility and lower oesophageal sphincter pressure. In both preterm[13] and term infants[14] the development of increasing tonic lower oesophageal sphincter pressure shows a close correlation with gestational and postnatal age. No such studies of oesophageal motility are however available. Carré's studies clearly indicate that in most infants with gastro-oesophageal reflux a developmental profile is followed that is different to infants who do not have reflux and would seem to most commonly be associated with delay of development of the mechanisms controlling lower oesophageal sphincter relaxation during swallowing.[1] In a few infants who have symptomatic gastro-oesophageal reflux the developmental delay is not confined to the lower oesophageal sphincter but also involves oesophageal peristalsis and may be very much more profound. As with other areas of the intestine the developmental processes concern both smooth muscle and innervation.[15] In a small proportion of the symptomatic infants reflux will occur as a result of disease. This is most obvious in pseudo-obstructive disorders where smooth muscle or the myenteric plexus is diseased or in cerebral palsy or tumour where defective extrinsic innervation results in a lax incompetent lower oesophageal sphincter. It is commonly held that a hiatus hernia is an anatomical abnormality, which results in more severe forms of gastro-oesophageal reflux. A hiatus hernia is a radiological description of the intra-abdominal segment of the oesophagus moving into the thorax, however, and is seen equally in infants with trivial or serious symptomatic reflux. Whether gastro-oesophageal reflux is trivial or serious is dependent upon the nature of the underlying disorder of oesophageal motor activity rather than the presence or absence of a hiatus hernia.

Investigation of gastro-oesophageal reflux

Investigation of the child suspected of having gastro-oesophageal reflux is in three stages: (i) demonstration of the presence and severity of gastro-oesophageal reflux, (ii) showing the presence of complications, and (iii) considering whether there are underlying disease states present that might give rise to gastro-oesophageal reflux.

(i) DEMONSTRATION OF PRESENCE AND SEVERITY

The 'gold' standard at the present time for detecting the presence and assessing the severity of gastro-oesophageal reflux is undoubtedly 24 hour ambulatory oesophageal pH monitoring with computerised data capture and analysis. Reliable microelectrodes for use in infants are now readily available and objective analysis of the pH recording using a number of variables including the number of reflux episodes of different specified durations, the time taken to clear refluxed acid, and the proportion of time during which pH is abnormally low have enabled reliable detection and assessment of the severity of gastro-oesophageal reflux.[16–18]

Other methods which are also used are barium meal and scintiscanning. Video or cine barium studies clearly illustrate disturbed oesophageal motor activity but gastro-oesophageal reflux may be missed as only intermittent exposures are made of relatively short duration. Compared with pH study gastro-oesophageal reflux is missed by barium study in about 40% of patients and severity can only be crudely and subjectively assessed. Gastro-oesophageal scintiscanning has been shown to be more sensitive than barium studies in detecting gastro-oesophageal reflux and also allows accurate quantities. It requires at least one hour recording, however, and the patient needs to be still.

(ii) SHOWING PRESENCE OF COMPLICATIONS

The complication of gastro-oesophageal reflux require a number of investigations for their detection: a blood count for iron deficiency anaemia, a chest radiograph, a search for fat laden macrophages in sputum where gastro-oesophageal reflux is suspected of causing recurrent respiratory disorder, and endoscopy with biopsy to detect oesophagitis. Where an anatomical problem such as a stricture, hiatus hernia, gastric outlet obstruction, or malrotation is suspected a barium meal should be given and followed through to the jejunum. Where gastro-oesophageal reflux is associated with fits or apnoea a pH study combined with apnoea monitoring, sleep studies, or an electroencephalogram as appropriate, may be very useful.

(iii) PRESENCE OF UNDERLYING DISEASE

A number of underlying diseases may give rise to gastro-oesophageal reflux as indicated above. Suspected pseudo-obstructive conditions will require specialist gastroenterological investigation. Gastro-oesophageal reflux that presents atypically may be the first indication of a cerebral tumour,[19] and thus computed tomography or nuclear magnetic resonance scanning of the brain may be required. The association of disturbed gastric emptying with gastro-oesophageal reflux is not entirely clear but it is well known that some 10–15% of infants with pyloric stenosis or malrotation will also have reflux. Thus barium examination must be continued to exclude these disorders. There is no place for a barium swallow alone to assess gastro-oesophageal reflux.

No single investigation provides all the information required for the management of gastro-oesophageal reflux. Ideally at least three are required: pH monitoring to detect the presence and assess the severity of gastro-oesophageal reflux, radiology for anatomical causes and strictures, and endoscopy to detect oesophagitis. These three factors will determine the nature and extent of the treatment required.

Management of gastro-oesophageal reflux

Gastro-oesophageal reflux may be controlled by a number of interventions, positioning, thickening of feeds, pharmacological agents, and surgery. The tendency for gastro-oesophageal reflux in infants to undergo spontaneous resolution by about the age of 18 months, however, has led to confusion regarding the indications for treatment and their merit.

Some indication of the type of treatment that is likely to be successful can be gained from a knowledge of the severity of the reflux. Patients in whom over 20–30% of a 24 hour period is spent with oesophageal pH below 4 almost always require surgery.[20] Whereas those with mild (5–10%) or moderate (10–20%) reflux will often be controlled by medical means until such time as development of the oesophageal smooth muscle and myenteric plexus has proceeded to the point where reflux is no longer a problem.

Mild gastro-oesophageal reflux or excessive 'possetting' or 'spitting up' will usually be controlled by changes in feeding practice and positioning. Giving smaller more frequent feeds is as helpful as the use of thickening agents. The two groups of agents most commonly used are carob seed preparations, Nestargel (Nestlé) and Carobel (Cow and Gate), and the alginate Infant Gaviscon (Reckitt and Colman). Infant Gaviscon also contains antacids, which give it a high sodium content and renders it unsuitable for use in infants under the age of 6 months.[21] Positioning is a time honoured treatment for gastro-oesophageal reflux but the practice of sitting infants up at an angle of 60% has been shown by several studies to be worse than leaving them supine. The most effective position is being prone with the head raised by 30 degrees.[18 22] Moderate gastro-oesophageal reflux is often associated with a degree of oesophagitis and antacids or H_2 blocking agents such as cimetidine or ranitidine are often helpful in controlling retrosternal chest pain. In this context Infant Gaviscon is often favoured by mothers as it is easy to give by just adding it to the infants feed. Drugs are also available that will directly reduce gastro-oesophageal reflux and improve oesophageal acid clearance. Those that are commonly used all have their effect on the myenteric plexus and include the cholinergic agonist bethanechol, and the so called prokinetic agents metaclopramide, domperidone, and cisapride. Bethanechol has unacceptable muscarinic side effects and is relatively ineffective.[23] The dopamine antagonists, metaclopramide and domperidone, both increase lower oesophageal sphincter pressure and enhance gastric emptying. Metaclopramide, however, also crosses the blood-brain barrier where it blocks dopamine D_2 receptors and may cause extrapyramidal disturbances by its effect on the basal ganglia. These effects are to some extent dose dependent and the total daily dose should not exceed 0·5 mg/kg body weight. Domperidone does not suffer from these disadvantages and is used in a dose of 0·6–1·2 mg/kg/24 hours in three divided doses. Cisapride, a new prokinetic agent, has its effect by modulating the release of acetylcholine from the myenteric plexus almost certainly by interacting with $5HT_4$ receptors. A recent study suggests that it also improves oesophageal peristalsis as well as increasing lower oesophageal sphincter pressure.[24] A dose of 0·6 mg/kg/24 hours in three divided doses has been used.

In those with severe gastro-oesophageal reflux management is often not successful. Surgery should seriously be considered in those infants who fail to thrive because their energy intake is reduced by recurrent vomiting, where oesophagitis is not controlled after three to four weeks of intensive medical treatment, where there is recurrent apnoea, chest infection, and haematemesis, and where a stricture has formed. The finding of a hiatus hernia with or without an associated partial thoracic stomach is not in itself an indication for surgery.[25] Gastro-oesophageal reflux may also be a cause of considerable morbidity in children who are severely retarded and in whom it is often misinterpreted or overlooked. Careful investigation and treatment may transform their lives. However, medical treatment is often ineffective and surgery is usually required.[26] The procedure most commonly used is a fundoplication with the Nissen variety being probably the most popular, which has a low mortality but some morbidity.[26] It is essential for adequate preoperative investigation to be done to assess whether there are associated anatomical problems such as a malrotation or disordered gastric emptying. In patients with these additional problems 'gas bloat', or more seriously acute gastric dilatation, occur more commonly postoperatively.

In the last decade the nature of gastro-oesophageal reflux and its association with the ontogeny of oesophageal motor function in the infant has been understood. More specific approaches to management are being developed but these require objective evaluation as to their indications for use and their efficacy.

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PERSONAL PRACTICE

Psychological guidelines in the management of paediatric organ transplantation

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Organ transplantation is increasingly being seen as the preferred treatment for several life threatening disorders of childhood. Though the early history of liver transplantation in the United Kingdom was not promising (only seven transplants were carried out on children under the age of 16 by 1983 and none survived longer than seven weeks), current one year survival rates exceed 60%.[1] Heart and heart-lung transplantation are now also available for some children, and increasing rates of success are being reported.[2] The advances that can be achieved are best seen in renal transplantation, in which the actuarial survival rate for children who received transplants between November 1968–December 1987 is 79% after 14 years, and for those who received transplants since October 1983, is 94% after four years.[3]

In the light of these results, teams are becoming increasingly aware of the need to implement practices that will enhance children's adjustment both in the short term and the long term. The purpose of this paper is to review the psychological issues encountered by children and families facing transplantation and highlight guidelines for clinical practice.

Discussing transplantation

In most cases it is possible to discuss the likely need for transplantation with the family. With the increasing technical success of renal transplantation it is becoming possible to take psychosocial factors into consideration when planning the optimal time for the operation, to maximise the quality of life for both child and family. The balancing of medical and psychosocial factors to make the operation as successful as possible is likely to become an important goal for all teams.

Gold *et al* identified two way in which parents may react to the information about transplantation that can present problems for teams.[4] The first entails being highly assertive, and is often reflected in having difficulties in relinquishing control of their child's management, seeking detailed information about the procedures to be undergone, and requesting second opinions. Medical and nursing teams alike find this both overdemanding and undermining, and it gives the families the appearance of being emotionally detached in their relentless pursuit of information. It is often at this time that mental health workers are asked to become concerned because of worries that the family may be denying the inevitability of their child's condition.

Despite the tensions that this style of coping sometimes produces, it is often one of the most successful ways of dealing with what might otherwise be overwhelming.[5] The pitfall for the medical team occurs when tensions become heightened to the extent that communication breaks down between them and the families. It is important that such families are recognised early on so that strenuous efforts can be made to form a working alliance by regular consultations, thereby promoting trust and confidence, and by keeping the parents as fully informed and involved as possible. In our experience it is also essential that the team nominates a key person, usually a senior member of staff, through whom communication with the family is filtered. This reduces the likelihood of friction occurring between members of the team and the family.

An alternative way of dealing with the news about transplantation is for families to become 'underorganised'. Because of their apparent compliance, these parents seem to present no overt concerns for medical teams. The pitfall is the assumption that the family have a clear understanding of the procedure and its implications. In general, patients' knowledge of body systems is poor. Fewer than half of adult patients know the location of important organs,[6] and many have misconceptions about their functions and how treatment relates to them.[7] In addition, their understanding of medical terms in common use is often confused,[6] and families commonly have questions that they feel too inhibited to ask. Bradford found that a third of patients on a liver unit failed to ask the questions that they wanted.[8] A common misconception for families is the anticipation that after transplantation their child will be 'as new', and as a result they minimise the continuing need for drugs and visits to hospital. It is only in discussing transplantation with the family, and through eliciting information rather than just imparting it, that the lack of knowledge and the misconceptions that they harbour become clear.

An issue that often confronts transplant teams is how much and in what way children should be informed of their illness and forthcoming operation. Evidence from paediatric oncologists suggests that the knowledge children have of their illness and the way in which it is acquired is associated with psychological adjustment in later life.[9] Children who were informed of their diagnosis directly and at an early stage—that is, within a year of diagnosis or by the age of 6 years—were better adjusted than those who were not told or who acquired the information through indirect channels such as by overhearing. Similarly, parents often want to know what they should tell the other children in the family. By studying the siblings of children who had died it was found that keeping a child informed of a brother's or sister's diagnosis and prognosis was an important protective factor in later adjustment.[10] Transplantation has a profound effect on every member of the family and efforts should be made to help parents recognise the need for open communication, which should clearly include discussion with their other children.

The way in which a child should be told about transplantation needs to take into account both the emotional and the cognitive development, because a child's knowledge about the body, its functioning, and the causes and prevention of illness and treatment, is related to the developmental stage. Preschool children tend to think that illness has a magical explanation or alternatively as being a result of their behaviour, usually a wrongdoing.[11] Consequently, treatment is often seen as a punishment. Primary school children think that illness is caused by germs or contamination.[10] Thus these children are likely to understand procedures such as barrier nursing but may fail to understand the need for immunosuppressive treatment and frequent blood tests. It is not until the teenage years that a clear concept of the body as a functioning system emerges.[12]

Surprisingly, research on doctor-patient interaction suggests that paediatricians often fail to speak directly to their patients.[13] It would seem therefore that doctors need to communicate more, particularly to reassure the preschool age group about the causes of their admissions to hospital and illnesses, to discuss anxieties about treatment with primary school age children, and to hold open and frank consultations with older children.

The prospect of a transplant obviously provokes anxiety. There is therefore a need to help children and their families discuss and cope with the forthcoming admission and procedure, and in particular to identify those who are most likely to adjust badly.[14] Factors that increase vulnerability include maternal mental health, poor communication and lack of cohesion within the family, lack of social supports, and a previous psychiatric history in the patient.[15]

Psychological interventions help to reduce distress for both child and parents, reduce the need for drugs, speed up the discharge, and improve the adjustment back to home life.[16] A number of techniques can be used to facilitate coping, including visits before admission,[17] videos of actors playing appropriate scenes,[18] organised play,[19] and by providing information and emotional support for parents.[15] Careful preparation before admission is clearly vital for transplant patients, many of whom will enter hospital at short notice. It is important that these families are made familiar early on with the ward and with the staff who will support them throughout their stay, but also that they should be prepared for the procedures, sights, and sounds they will experience. Scrap books and photograph albums of other children during various stages of their treatment can be invaluable aids that are relatively easy and inexpensive to provide. It may also be helpful to offer written advice about what practical steps need to be taken to prepare for admission.

During this period the team will want to foster a positive attitude in the family about the forthcoming operation. The reality that some procedures are unsuccessful, however, also needs to be acknowledged. The team needs to be aware of and plan for the support the family will require if the operation fails and the child dies, as well as the profound effect that such an event has on staff and other families on the unit. The bereaved family will often look for support during this period to those members of staff whom they already know. It is important to recognise that a main source of stress among staff is the sense of impotence that they feel when they are unable to relieve the distress of parents who have lost a child. Woolley *et al* identified particular issues of staff finding parental anger, as part of the grief response, being difficult to cope with.[20] It is advisable therefore that all members of the team, including the most junior, should be familiar with the processes of grief, and know what to do when faced by grieving parents and siblings.[21] In our experience it is important that the members of the unit have the opportunity to explore their own feelings about the loss of a child. Where this is seen as too threatening or inappropriate it is possible to approach the topic by offering a structured session on the psychology of death and grieving. This usually opens out into a discussion of events on the unit and allows staff to deal with their own feelings at their own pace.

After transplantation

IMMEDIATELY AFTER THE OPERATION

After transplantation children will spend variable amounts of time in the intensive care unit. Though there is little evidence about the emotional effects of being in an intensive care unit on children, there have been a number of studies of parents' reactions. Specific areas of parental concern include the sights and sounds associated with the physical environment such as monitor alarms, equipment, and other ill children. They are worried about the child's appearance, mood changes in older children, procedures carried out on their child, such as the taking of blood, the insertion of catheters and cannulas, and physiotherapy treatment. Parents are concerned about staff behaviour and communications including the use of jargon, levity, and apparent remoteness; how they should behave in relation to their child and the lack of a clear role; and the child's behaviour, when this included confusional states, demanding, or inactivity.[22] These authors advocate the need for clear communication about what to expect and what the parents' role is.

A common complication immediately after the operation is infection and the need for barrier nursing. The isolation associated with this form of treatment can lead to the child reacting with anger towards staff and parents, poor compliance, and tearfulness. Structuring the child's day so that boredom and loneliness are minimised, as well as ensuring that the child can communicate, is an essential part of nursing care. This can include incorporating free play periods with nursing staff who may otherwise have limited contact other than during aversive procedures, the creative use of video and television give the child access to what is happening outside the room, and communication with peers by audio tapes.

A number of psychological techniques have been developed to help children cope with specific medical procedures. These include giving the child clear signals and advance warning that a procedure will take place by—for example—explaining that blood will only be taken when the nurse wears a red badge, helping the child to take part in the actual intervention,[23] teaching relaxation by breathing exercises and imagining pleasant scenes,[24] acting out scenes of effective coping and talking positively,[25] and using the child's ability to imagine a favourite character, such as Super Ted, dealing appropriately with such circumstances. In addition, staff can increase the child's compliance by rewarding good behaviour during procedures with star charts, bravery certificates, and badges.[26]

In the weeks after transplantation it is not uncommon for children to experience changes of mood including unhappiness, crying, and mild depression, which in most cases reach a peak about a month after the operation.[27] Parents should be warned about this, both to ameliorate the child's distress and decrease their own anxiety. It may also help parents to achieve an appropriate balance in their approach to their child. A particular concern at this stage of the child's recovery is infection. For patients who have received liver transplants this is a common complication that serves to highlight for both child and parent their continuing vulnerability. It can also arise in patients who have received kidney transplants and who, despite previous information, regard the failure of the graft to provide adequate function immediately as an ominous sign. The emotional state of both parent and child is usually closely related to the course of the medical condition, with disturbance being associated with periods of infection, rejection, and poor functioning of the graft. This continuous raising of hopes matched by periods of disillusionment can result in conflicts developing and becoming overt, expression of anger, and even distancing from the patient. The process may be mirrored within the team treating the child, with staff adopting polarised positions in relation to the child's continuing treatment. Ideally these conflicts need to be acknowledged and steps taken to reach a consensus. The reality is often more complex because of the differing burdens of professional responsibility.

AT THE TIME OF DISCHARGE

As the child's medical condition becomes more stable, the team becomes increasingly aware of the need to help the child back into a more normal pattern of life. Of particular concern to both parents and children are the problems of losing contact with peer groups, falling behind with schoolwork, and the types of restrictions that may be imposed on the child's physical recreation. Brookes reported that the child's return to school after the operation is often most stressful,[28] and clearly this needs to be planned in advance. In addition to children and parents this process should include teaching the staff both from the hospital and the school, as well as doctors, to provide accurate information on the child's needs and abilities and to dispel myths and reduce anxieties about the child's vulnerability. Overprotection by others is a common problem for children with chronic disorders, and this is also true for children with transplanted organs.[27 29]

It is therefore important that medical staff actively inquire about the child's acquisition of an appropriate degree of independence when seen for follow up.[8] Where it is possible for teams to work in a multidisciplinary fashion much of this kind of follow up is appropriately carried out by other, non-medical, members of the team such as teachers, who may be able to approach the child's school to get a wider picture. If the team do have concerns about the adequacy of the child's development, training in particular skills and graded behavioural programmes like those that have been developed for adolescents can be helpful,[30] as well as family treatment.[31]

Long term management

Long term success of organ transplantation depends on adherence to medical regimens and treatments over extended periods of time. Noncompliance can be a considerable problem, particularly in young teenage recipients. Fine reported that three quarters of the recipients of renal transplants who admitted to not taking their drugs subsequently lost their graft (R Fine. Non-compliance in paediatric patients with chronic renal failure. Paper presented at 20th annual conference of European working group on the psychosocial aspects of children with chronic renal failure. Hanover, 1989). Much work has been done on this problem, the main variables being (a) the characteristics of the treatment regimen: side effects, duration, and complexity; (b) the doctor-patient relationship: dissatisfaction with consultations, and long waiting time; (c) family factors: instability or discord, poor communication, lack of support from family members, maternal mood, poor maternal understanding of treatment, and lack of supervision. Other variables are individual characteristics: age (adolescence), sex (female), poor understanding, perceived vulnerability and doubts about the effectiveness of the treatment, and psychological problems before treatment.

A number of approaches aimed at increasing compliance have been described.[32] It is worth approaching the problem step by step, firstly by addressing the patient's understanding and active misconceptions about regimens of treatment. If it is clear that the patient has not understood the requirements, compliance can be improved by: reducing the complexity of the regimen, and providing written supporting material, either in the form of a handout or a booklet that the patient keeps. Should the educational approach be insufficient, the second step is to assess the motivation of the young person or family. With adolescents, where the attainment of autonomy and independence are uppermost, it is sometimes possible to manage the problem by increasing the patient's sense of control by negotiating which drugs they need to take and when, coupled with increased medical supervision. In teenage girls noncompliance is commonly associated with cosmetic side effects such as excessive weight gain, cushingoid features, and hirsutism. When possible the team needs to help the child solve these difficulties within the context of adequate medical treatment—for example, by using an alternative immunosuppressive drug, providing dietary advice, depilatories, and other cosmetic measures when the problem is severe. Finally, psychological or family issues may play an important part, necessitating referral to other specialists.

As transplantation programmes become increasingly successful, the assessment of quality of life is becoming more important.[34] For example, patients who received liver transplants need fewer admissions to hospital and drugs than they did before operation, their growth and general development have increased.[35] Other studies have highlighted some children who have persistent delays, and point out that positive outcomes such as catch up growth are usually determined by factors such as age, height, and bone age before the transplant.[36]

It is often assumed that children who have received transplants have serious mental health problems but the evidence is inconclusive. Children who have received liver transplants have been described as having appreciable psychological problems,[29] whereas most children with renal transplants are said to be well adjusted on formal psychiatric and psychological assessments.[37 38]

There is also a suggestion that children have emotional problems in accepting and integrating the new organ. On balance the evidence does not support this, although cases of children experiencing difficulties do occur. They tend, however, to be children who had emotional problems before the transplant, and in these cases the transplant is likely to colour the way in which distress is manifested rather than be a causal factor in itself.

There is firmer evidence that children with transplants feel differently about themselves compared with most other healthy children, particularly in terms of self esteem and body image. Many authors comment on the children's sensitivity about the physical changes caused by immunosuppressive drugs, their reactions to scars, their persisting short stature, and deformities caused by bone disease.[37] It is important to identify dissatisfaction with body image early on, as follow up studies suggest that such difficulties are associated with problems of emotional and social adjustment in later life.[28 38]

Parents report difficulties in achieving an appropriate balance between protectiveness and independence at this stage. The main areas of concern are re-establishing old family patterns of interaction, coping with worries about the future, and the side effects of medication.[4] A particular stress is the death of another child, as this can reawaken their own sense of vulnerability. In the case of renal transplantation, failure of the graft necessitating a return to dialysis is a similar factor. Evidence suggests that when good functioning of the graft is established, normal family routines reestablish themselves within a year.[39] Studies of families in which a child has received a liver transplant suggest that parental problems in adjustment are more entrenched.[4 35] This is possibly because of the higher incidence of rejection and complications, as well as the lack of alternative treatments if transplantation fails.

The above arguments indicate a need for regular psychosocial reviews to be built into the medical outpatient assessment, so that problems can be identified early and appropriate help provided. There are critical transition points in the life cycles of families that can delay successful adaptation. Consultations need to focus not only on medical aspects, but also more general issues, such as how the family are coping and whether the child's development is appropriate for age, as it is only in integrating psychosocial and medical factors that optimal care can be provided.

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MEDICAL EDUCATION

Examinations in paediatric training

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The examination system in the United Kingdom that is an integral part of the training of paediatricians is often the subject of heated criticism. Whether the emotional energy behind this is fed by prejudices arising from traumatic experiences in their early careers, or by commendable concern for their juniors' unexpected difficulties, is for individual paediatricians to decide. There can be no doubt that there is an enormous expenditure in time and money in both setting and sitting these examinations. To consider this subject dispassionately it is essential to share a clear understanding of the main elements of the discussion. Experience of the United Kingdom examination system for both undergraduates and postgraduates will be used to illustrate the attempts being made to answer some of the questions shown in table 1.

Table 1 Questions to be discussed when assessing the role of examinations in training

- What are we trying to achieve in training in paediatrics?
- How important are examinations?
- What constitutes a 'good' examination?
- How can examiners be helped to conduct useful, fair examinations?
- How can candidates best be helped to pass these examinations?
- How can the system be kept flexible enough to:
  (i) adapt to changing professional requirements, and
  (ii) to use advanced educational techniques as they arise?

Training in paediatrics and the examination system in the United Kingdom

Undergraduates are taught paediatrics in university departments as a compulsory part of their medical courses according to the regulations laid down by the General Medical Council. In most universities, however, the final examination in paediatrics is merely a part of the final examination in medicine. After qualification, there is a fork in the path of further paediatric training, one branch leading towards a career as a consultant paediatrician and the other towards a career as a general practitioner with a particular interest in primary care paediatrics. Those aiming for a future consultant post take the two parts of the Membership of the Royal Colleges of Physicians (MRCP). Trainee general practitioners and clinical medical officers may take the Diploma of Child Health (DCH) of the Royal College of Physicians of London or of Glasgow, or the Diploma of Community Child Health (DCCH) in Edinburgh. Those training in specialties close to paediatrics such as child psychiatry, paediatric surgery, anaesthetics, and paediatric pathology may take either the paediatric option of the second part of the MRCP, or the DCH, to strengthen their claim that they have a special interest in paediatrics.

Aim of training in paediatrics

The minimum target of training is that every qualified doctor should be aware of the differences between sick children and sick adults. This should reduce delays in diagnosis, reduce the risk of inappropriate treatments, and modify the emotional trauma to the child and family during illness. Every doctor should also be aware of the special needs and vulnerability of children, and know how to help or protect them. These topics should be covered during the undergraduate course, which should also emphasise the association between paediatrics and basic medical science.

Role of examinations in training

There are two opposing opinions about the role of examinations in training. These can be compared with the 'carrot' and 'stick' methods of activating an obstinate mule. On the 'carrot' side is that the examination is a method of concentrating attention on the subject or task so that candidates may obtain feedback about their performances compared with expected criteria or the performances of peers. This can then be used as a guide to filling in important gaps in knowledge or skills.

The 'stick' side is that the examination is a hurdle to test the motivation of the trainee, a forced compliance with an imposed set of tasks from which a feedback of merely 'satisfactory' or 'unsatisfactory' is given. The gate to the next stage in the career is opened or remains closed, depending on the result of the test. When viewed from these poles, it is clear that examinations that generate feedback must be relevant to the content of the training course, whereas a hurdle can have any content of which the candidate has been warned. In a competitive popular specialty, any hurdle that tests some of the above attributes of the future specialist could be defended as an invigorating example of survival of the fittest.

Many trainees and students will ask for examinations as a target for managing the timing of their studies. Many teachers will depend on the results as a form of evaluation of their methods of teaching and course design. The wider community insists on an objective assessment of competence to ensure that standards are maintained and that new methods of training are not producing unacceptably different groups of professionals.

Design of examinations and quality control

The ideal examination would (1) be highly relevant to the content of the training course; (2) require a method of study or working that develops skills or attitudes necessary for future professional life; (3) encourage the trainers to provide appropriate teaching, time, and facilities; (4) test that the trainee had reached the expected standard of attainment of professional attributes for that particular stage of training; (5) be comparable within and between groups of trainees; (6) be objective, requiring little personal judgment by individual examiners; (7) be conducted by carefully trained examiners whose performance is checked; (8) specify areas of strength or weakness that would guide further training; (9) recognise incompatible attitudes early and match with more appropriate specialties for career guidance; and (10) evaluate the training scheme and suggest modifications. The range of methods of examination includes continuous rating by trainers, tests and tasks during the course, projects to work on, and preparation of a thesis, as well as essays, modified essay questions, multiple choice questions, case commentaries, interpretation of data, recognition of slides, computer assisted interaction, and oral and clinical examinations.

Some of the types of examinations being used at present are given below, and the reader may judge the content of these against the above ideal.

UNDERGRADUATE PAEDIATRIC EXAMINATIONS

Whether as a formal separate examination or as a part of the final examination in medicine, paediatrics is tested towards the end of the undergraduate clinical course as well as at the end of the paediatric attachment or course. Many departments require their students, individually or in small groups, to complete a project on a subject connected with child health. These entail reviews of published work, the design of questionnaires or surveys, how to deal with patients and parents, analysis of results, and then either written or verbal presentations, or both. Some of the most successful projects have been awarded prizes by the British Paediatric Association and have been received with acclaim by paediatricians. Project work is clearly a forerunner of future professional activity; it teaches teamwork, and methods of retrieving, analysing, and presenting data, as well as generating an active and creative learning approach. It is doubtful whether the students would be able to overcome the inertia of starting a project without the certainty that it will eventually be assessed.

Most people who teach paediatrics to undergraduates grade their students at the end of their attachments. The subjectivity of this process and the dangers of seeming to favour those students who may be known to the teachers through sports, music, or committees, can be reduced by the use of tests during the course. Many departments use multiple choice questions to assess ability to recall facts, oral examinations to test ability to solve problems and some communication skills, and clinical examinations to check on how students deal with patients and skills in examinations. The student's motivation and powers of reasoning and judgment are best evaluated by their paediatric tutor who has provided the opportunity for more detailed discussions. Feedback and advice at the end of the course is often neglected, but may help the students greatly in their future consideration of paediatrics and in their progress through the rest of their undergraduate courses. Their teachers must remember, however, how vulnerable these young students are not only to any sarcasm, but also to distressing clinical experiences. Sometimes poorer than expected performances may indicate that students require help to come to terms with issues arising from their experiences with sick children.

POSTGRADUATE EXAMINATIONS—DIPLOMAS IN CHILD HEALTH

The Diploma of Child Health (DCH) of the Royal College of Physicians (London) is a good example of how it is possible to alter an established examination to accommodate a changing need. Originally the DCH was taken in addition to the MRCP by trainee paediatricians; a large number took the MRCP and only then indicated their special interest in paediatrics by sitting for the DCH. The content of the examination then reflected the orientation of paediatrics in hospitals. The MRCP now has a paediatric option in the second part, and most paediatricians take this. More trainees in general practice, however, who were inspired by their contact with paediatrics during their six months post during vocational training, opt to take the DCH. Most candidates for the DCH of the Royal College of Physicians (London) are trainees in general practice, with a few from community paediatrics, hospital paediatrics, child psychiatry, paediatric surgery, and anaesthetics.

The DCH comprises a preliminary test of 60 multiple choice questions, which excludes the weakest candidates from taking the clinical part of the examination. The content of the multiple choice question test is mainly primary care or preventive child health. A written test has questions that require only short answers on common primary care paediatrics, a question about a case commentary focused on community or chronic paediatrics, and another on more acute child health problems. The questions are set by a panel made up of general practitioners, hospital based paediatricians, community based paediatricians, paediatric surgeons, and child psychiatrists. The clinical part is examined by the same balance of specialties, and includes a long case, during which the candidate takes a detailed history from the parent and child, carries out a full clinical examination, and then presents the findings and discusses management and communication issues with two examiners.

A different pair of examiners then takes the candidate round a series of children with physical signs. They pay special attention to the candidates approach to the children and technique of physical examination. Developmental testing is also evaluated during this part of the DCH.

A great deal of effort goes into selecting subjects relevant to primary care paediatrics for the multiple choice questions and questions requiring only short answers. Each question is tested for its discriminating power (that is, how well do candidates score on the individual questions correlated with their scores on the whole test). Questions that discriminate poorly can then be modified, usually by removing any ambiguity of the language or making the question slightly easier. Although individual candidates who fail are offered advice, there is no detailed feedback of poorly answered questions, or reports to the candidates of weak or misunderstood areas. With the increasing use of modern technology and increasing 'glasnost' of examining boards, more detailed feedback may be forthcoming.

An analysis of the behaviour of the various types of professional examiners in the DCH examination showed that they were of similar generosity or meanness in their awarding of marks. When the written papers were marked by two examiners there was a clear similarity in the marks given.

The DCH of the Royal College of Physicians (Glasgow) also comprises a written paper on the principles of child health with particular reference to community child health, and clinical and oral examinations.

The Diploma of Community Child Health (DCCH) is jointly managed by the Royal College of Physicians (Edinburgh), the Royal College of General Practitioners (RCGP), and the Faculty of Community Medicine (Public Health) of the Royal Colleges of Physicians of the United Kingdom.[1] The DCCH comprises an assessment of written case reports submitted by the candidate, a written paper with a modified essay question with six to 10 sequential questions, and 10 to 20 questions requiring short answers. There is an oral examination but there was no clinical examination until the 'objectively structured clinical examination' (OSCE) was introduced. Some clinical skills are assessed with written questions about material on still photographs or video sequences.

An important question to ask is whether the DCH or DCCH are driving the studies and the demand for experience of the trainees in an appropriate direction. Clearly the emphasis on primary care is valuable and by including developmental, vision, and hearing testing in the clinical examination it has encouraged the trainees to become familiar with these essentials of developmental surveillance. There are a number of general practitioners and paediatricians, however, who feel that these diplomas give inadequate confirmation that a trainee general practitioner has reached a sufficiently high level of competence to carry out child health surveillance.

POSTGRADUATE EXAMINATIONS—MRCP (PART I)

The MRCP (Part I) is a paper containing 60 multiple choice questions that aims to test a broad knowledge of medicine. It includes questions about basic science, and also about particular diseases, and includes psychiatry and paediatrics. The questions are set by an examining board that has representatives from the three Royal Colleges of Physicians of the United Kingdom, including at least one paediatrician, a psychiatrist, and consultants in general medicine. The balance of the questions is decided by the examining board, and the discriminating power for these multiple choice questions is also analysed in the same way as described for the DCH. It is acknowledged that multiple choice questions inevitably test recall of facts, and only rarely touch on slightly higher levels of reasoning and judgment. They also have the disadvantage of giving a clue to the answer but the candidates do have to make a clear decision between 'true' or 'false' or accept that they do not know. They are penalised with a negative mark if they guess unsuccessfully. It could be strongly argued that this penalty for not honestly admitting one's ignorance is an appropriate feature of an examination that is an entry test for consultant training.

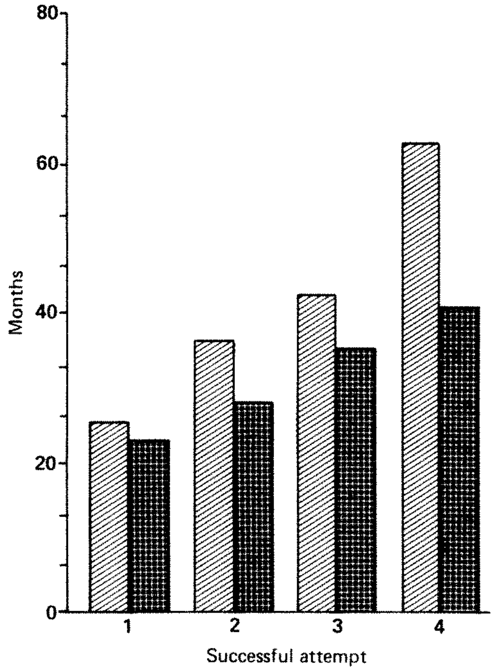
Paediatricians seem to feel more unhappy about the MRCP (Part I) examination than about any other educational issue. There is a fear that it is unfair to those who intend to become paediatricians, although they acknowledge that it is usually taken by senior house officers (SHOs) before they have travelled far into their specialist paediatric training. The main anxiety is that if it is competitive, the paediatric SHO who is first on call and frequently deprived of sleep (especially in neonatalogy) is at a disavantage compared with the medical SHO who is shielded by preregistration house officers. There is also concern that the examination might pose difficult questions about diseases associated with psychogeriatrics or other specialties with which the paediatric trainee is inevitably out of touch. A study was therefore carried out by the MRCP (Part I) Board to look into some of these anxieties and to consider whether any changes were indicated.

A previous study carried out between 1972 and 1976 showed that those candidates who eventually took the paediatric option in Part II had a similar rate of passing Part I at their first attempt as those later opting for Part II in general medicine.[2] Those who eventually took the paediatric Part II, however, had taken significantly longer than those who took the Part II in general medicine (average 34 months from qualification compared with 27 months, respectively).

In the recent study the results at Part I for the 290 entries to the paediatric option at Part II and the results for the 1490 general medical entries during the year 1989 among graduates from medical schools in the United Kingdom were compared. Again the future paediatricians had taken longer to obtain their Part I passes than those taking general medicine (average 37 months compared with 27 months, respectively, in 1989). When this was analysed further, it appeared that it was partly because more paediatricians required more attempts to pass

Table 2 Entrants for the paediatric option for the second part of the MRCP in 1989 compared with those who took the general medical option for the number of times they took the first part before they were successful

No of attempts at Part I before passing	*No (%) who took the paediatric option*	*No (%) who took the general medical option*
1	103 (36)	767 (52)
2	96 (33)	438 (29)
3	55 (19)	195 (13)
4	36 (12)	90 (6)
Total	269 (100)	1490 (100)



Interval between qualification and success in the first part of the MRCP examination. The striped bars represent those who took the paediatric Part II, and the cross hatched bars those who took the Part II in general medicine.

Part I (table 2), and partly because paediatricians waited longer to make these attempts if they were unsuccessful on the first attempt (figure).

Table 2 shows that the paediatricians took significantly more attempts to pass Part I than the general medical candidates. When all the Part I scores for all attempts for the 290 paediatric entries and the 1490 general medical entries were considered, the mean was 58·22 for paediatricians and 60·48 for those doing general medicine.

The delay in making further attempts to pass Part I can only further disadvantage paediatricians, so they should be given all the help they can to take Part I as soon as possible.

As part of the study for the MRCP (Part I) Board, this small but real disadvantage was investigated by a paediatrician, who analysed the content of the items of nine Part I papers between 1983 and 1990. Items were judged according to their advantage or otherwise to paediatricians (table 3).

The report of this study has recently been discussed in depth by the Royal Colleges of Physicians of the United Kingdom and the recommendation of the Part I Board to reduce this small imbalance has been endorsed. It is planned to increase the number of 'no disadvantage' questions from 62%, and to balance the 'clear advantage' questions as much as possible in future. A shortage of multiple choice questions on important paediatric topics that would be fair to ask the general medical candidates is slowing down this process, and paediatricians are invited to supply material either to the British Paediatric Association or directly to the Royal Colleges of Physicians.

Table 3 Analysis of the content of 2700 multiple choice questions in the MRCP first paper for potential advantage or disadvantage to trainee paediatricians

Degree of advantage	*Percentage of items*
Clear paediatric disadvantage	15
Some paediatric disadvantage	9
No disadvantage or advantage	62
Some paediatric advantage	5
Clear paediatric advantage	9

POSTGRADUATE EXAMINATIONS—MRCP (PART II)
Trainee paediatricians have an option when they have succeeded in MRCP (Part I) to take the Part II in paediatrics. The examination consists of a written paper, which is made up of questions about interpreting data, case commentaries, and projected material. This written paper achieves a fair degree of objectivity as marking keys are given to the examiners who meet in groups to score, which allows for unexpected responses from candidates to be discussed and awarded a reasoned mark.

To increase the value of the MRCP (Part II), paediatricians are invited to supply case histories, results of investigations, and clinical photographs of children by whose cases they felt that they had been tested, whether they were successful or not. This would aim the questions at subjects that are testing for practising paediatricians.

Writing and editing questions based on this material is time consuming and rather daunting the first time. Paediatricians are requested to send even raw case material to the Royal Colleges of Physicians or the British Paediatric Association for processing into questions of the usual type (and more innovative questions for the future) where they will be edited and then sent on to the examination boards and question groups of the Royal Colleges of Physicians. When their questions are used, members will be notified about how the candidates did, and how discriminating their questions were.

Sharing the responsibility for evaluating training and trainees

Supplying clinical material and questions to examination boards, agreeing to become examiners, helping to host clinical examinations in hospitals, and practising being examiners with junior staff and students, will all help in maintaining a fresh and relevant examination system. The Royal Colleges, but perhaps less so the universities, take care to pair an experienced examiner with a less experienced one. Most examination boards keep a check on any extremes of marking by examiners by feeding back the examiner's place on a 'hawk-dove' scale. More junior paediatricians should be trained to examine, and this is equally true for other essential techniques in medical education. Little encouragement is likely to be given to junior academics to develop these skills, however, if they compete with time for research.

Helping trainees to pass examinations

Helping the trainee to pass one of these examinations is an obligation on the trainer; paediatricians are beginning to recognise what general practitioners have known and practised for sometime. The junior paediatric grades are training grades and time should be allocated to teach, appraise, and coach. This is a fair trade off for the reduced workload of consultants fortunate enough to have adequate junior staff, and is an extremely useful way of keeping up to date. This effect of the system is often forgotten in the discussions about whether examinations are necessary or desirable.

Another important contribution to training and continuous medical education is the production of teaching material and review articles in journals. It has always surprised me that so little time is allocated in annual meetings of the main scientific associations to teaching sessions, which would provide valuable 'updates' for practising paediatricians who would return to their trainees armed with the most modern understanding of the management of important clinical problems.

Maintaining flexibility of examination system

Fortunately the universities and Royal Colleges are aware of the changing nature of medical practice and the role of the doctor in health management. What is less evident is the response to new techniques. Few examinations include videos of important physical signs, which might be too transient or too distressing to have as short cases. Interactive management of problem cases could be constructed by combining the existing parts of the written examinations of the DCH or MRCP, but the fear of computers is collaborating with the normal inertia of accepting new techniques.

Conclusion

Examinations are necessary for feedback to trainees and to ensure a standard of proficiency, especially in dealing with ill children. The DCH examiners are exorted to reject doctors who they would not want to treat their own children. We should all share the responsibility of making the examination system work in favour of children by providing them with well trained and tested doctors who have not wasted their time learning unnecessary trivia.

I thank Dr Peter Fleming, Chairman of the Part I Board, for encouragement, Dr Alastair Vale, Secretary to the Part I Board for checking the Part I statistics, the examinations and computer departments of the Royal College of Physicians for finding the data, to the Presidents, Censors, and Officers of the Royal Colleges of Physicians in the United Kingdom for their permission to publish the results, Dr Bill Uttley for information on the Edinburgh Diploma of Community Child Health, and the Board and examiners of the London Diploma of Child Health for their help in the various studies of examiners' performance.

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Archives of Disease in Childhood 1990; 65: 1009–1010

PERSONAL PAPER

Senior house officer posts in community paediatrics —an introduction to child health

Jan Welbury, Arthur Paynter, J M Parkin

The need for paediatricians and general practitioners to have had experience in community child health during their training is acquiring a high priority. Training posts in community child health have been available in the Northern region since 1979. They are modules on the paediatric senior house officer (SHO) rotation, or open to individual appointment, and are described and their training value discussed.

The *Court Report* recommended that the tripartite health service for children should evolve into an integrated service, with preventive and surveillance aspects of preschool child health being undertaken by primary care teams, and specialist aspects of community child health becoming the responsibility of consultant led teams.[1] The concept of surveillance within primary care is now supported by both the new contract for general practitioners[2] and the report by Hall.[3]

This fundamental change has training implications for both primary care and paediatrics and programmes are being designed to meet their needs. Colver *et al* have described a programme for senior registrars in community paediatrics,[4] and Polnay and More have described a three year general professional training in community child health.[5]

All trainees in paediatrics now are recommended to have some experience within the community. It is arguably more appropriate for those entering general practice to have experience in community than in hospital paediatrics, although a combination of the two is probably the most desirable. In fact at the present time 40% of vocationally trained general practitioners can be offered neither postgraduate hospital nor community paediatric experience.[6]

In the Northern region, full time community child health experience at SHO level, as opposed to comprehensive training,[5] has been available since 1979. Seven districts have created 10 posts: eight for six months and two for one year. Three of the former and one of the latter have formal acute on call commitments in the local paediatric units. All the posts are funded from community health budgets.

The content of the posts, and hence their eligibility to be included in the scheme, is monitored by the regional education committee for community paediatrics. Supervisors who are specialists in community medicine or child health, senior clinical medical officers, or consultant community paediatricians must be approved by this committee. At the end of their appointment the trainees are asked to complete a questionnaire to ensure that standards of training and supervision are maintained.

The Education Committee for Community Paediatrics in the Northern region
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Description of the posts

The paediatric experience of the trainees varies widely. Some are SHOs on a paediatric rotation or general practitioner trainees who have had experience in primary care, obstetrics, and on occasions paediatrics, while others are newly registered doctors joining a training scheme. The individual posts are not tied to any particular SHO rotation but those requiring an acute on call commitment attract and are given to doctors with previous experience.

SERVICE EXPERIENCE

The trainees are attached to and supervised by a senior community doctor and share in their service commitment. This includes preschool surveillance and immunisation in the local authority child health clinics and school health in mainstream and, where available, special schools, including assessments under the 1981 Education Act. Other service commitments vary between districts but experience in the care of children with special needs, in the field of abuse, and in liaison with social services are seen as important. Other experience, for example services to hearing and visually impaired children and fostering and adoption, varies with availability. At this level of training there is little if any experience offered in committee work, service development, or personnel management, but the philosophy and practice of good interdisciplinary work is emphasised. Small projects are encouraged particularly in the one year posts and have often proved to be of value to the districts.

ORGANISED TRAINING

The more formal training components of the scheme include a course for one week on child development at the beginning of the appointment, and a weekly afternoon seminar organised by a tutor who provides continuity. All trainees must be allowed to attend these sessions, participation in other courses being at the discretion of their supervisor. The initial course is designed to give a theoretical grounding in the principles and practise of child development and surveillance. The afternoon seminars cover a wide range of topics and give the trainees the opportunity to compare differences in service provision between districts. An important function of the seminars is to provide the trainees with the chance to meet regularly in what could otherwise be an isolated post.

Evaluation of the posts

Between 1979 and 1987, altogether 90 doctors passed through the scheme. In order to evaluate the posts questionnaires were sent to as many as could be traced. These asked for information about career intentions at the time of taking up the appointment and at the time of the survey, the relevance of the post to their career, the training value of the post, the adequacy of supervision, the appropriateness of the formal teaching, and whether they had enjoyed their attachment.

Forty seven doctors returned completed questionnaires; 38 had held six month posts, although nine of these stated that they would have preferred a year post. Twenty of the respondents were on a paediatric rotation. Of the 26 prospective hospital paediatricians, 20 had continued in their chosen career, five had moved into community paediatrics, and one had become a general practitioner. One prospective community paediatrician had become a hospital paediatric consultant. Twelve general practitioner trainees had continued in family practice and two doctors had moved into fields unrelated to paediatrics.

On the whole the responding doctors had enjoyed their appoinments, valued the training input, and felt that the experience had been beneficial to their subsequent careers. There was, however, a mixed response to the questions about supervision and formal training. Some trainees commented on a lack of supervision and support. From these replies those districts where supervision was a problem were identified and their difficulties addressed. The education committee has also recently developed and recommended a system of counselling, the trainees being seen formally by their supervisors twice in a six month period for a semistructured assessment and discussion.[7]

There seemed to be two possible contributing reasons for this lack of satisfaction. The first is the contrast for trainees between the traditional hospital model of consultant led supervision with readily accessible support, and the relative isolation of doctors working in the community. The second is the inexperience of many community doctors in teaching and supervising junior staff.

The one week introductory course was much appreciated, though response to the afternoon seminars was variable probably because of limited time to cover all important topics.

Trainees appreciated the opportunity to gain experience in developmental paediatrics and to work in depth with children with special needs. Working within a multidisciplinary system and gaining a new perspective about the influence of social and environmental factors on health and illness were also seen as valuable. Being away from acute hospital commitments and having time to read and reflect were noted to be extremely educative and liberating.

On the negative side it was felt that there was insufficient opportunity to participate in the long term management of children with special needs and those suffering child abuse and neglect. Trainees also felt the need for more structured training in epidemiology and would have liked to carry out a research project. These criticisms are acknowledged but are difficult to address within a six month appointment. Some trainees perceived a failure of the system to tackle behaviour problems and the lack of integration and liaison of the community service with the hospital service and primary care.

THE RESPONSE OF THE SUPERVISORS

Supervisors were questioned about the impact of a trainee on the district service. On the whole the response was favourable, the presence of the trainees being thought to be stimulating. The usefulness of the SHO in service was small in the early months, however, and short lived in the six month appointments. Continuity, particularly in school health, is often vital and so the contribution of the SHOs to that service was thought to be limited.

The one year posts were much more valuable to the community service, but the education committee are anxious to maintain the six month appointments to ensure availability of community experience to the maximum number of trainees. It is also of note that normally only six months of community paediatrics is recognised as contributing towards general professional training.

Conclusion

Experience in community paediatrics is considered to be of value in the training of paediatricians and family practitioners. A system of providing this experience has been used in the Northern region over the past 10 years, utilising the existing community child health services. It cannot be and does not claim to be a comprehensive training programme. It does allow the development of basic skills in community child health, however, and gives insight into children in their normal environment and also into the paediatric services in the community.

The pattern of training is evolving. As consultant led community child health takes on more of a secondary care roll, these appointments are beginning to include some sessions with primary care teams carrying out preschool prevention and surveillance. However, we anticipate that they will continue to provide useful and valid training experience for both general practitioners and paediatricians.

We acknowledge with gratitude the role of many senior community doctors who have been supervisors and at some inconvenience have welcomed a series of SHOs into their team. These include: Dr A Carruthers, Dr AF Colver, Dr MJ Danskin, Dr P Halse, Dr KM Kirby, Dr RJ Menzies, Dr R Mitchell, Dr FS Rogers, and Dr A Waterston.

Sadly Professor JM Parkin died on 11 February 1990.

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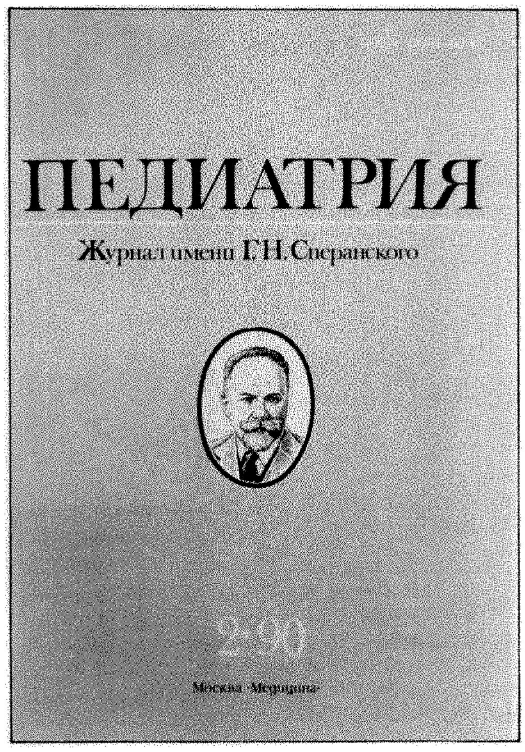
ІЕДИАТРИЯ



ПЕДИАТРИЯ

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Москва Медицина

Pediatriia 1990.

One tiny result of Mikhail Gorbachev's idea for a 'common European home' is the agreed exchange of the *Archives of Disease in Childhood* for issues of *Pediatriia*, the journal of the Paediatric Association of the Soviet Union. I have looked through the first two issues of 1990. I have no Cyrillic and less Russian, and therefore studied the English elements: contents pages, summaries on the major articles, and the occasional western references printed in roman script.

At the immediate level there is little to suggest that the general paediatrician in Britain would have his or her practice improved by receiving full translations of most of the articles. Their summaries tend to have a somewhat old fashioned tone. Phrases such as 'Children with a history of grave asphyxia need rehabilitation treatment aimed at the recovery of psychomotor function' or 'intestinal microbiocenosis in the newborn turned out to be more physiological provided they were placed in the "mother-child" department as compared to that where the newborn stayed alone' do not instantly whet the appetite. On the other hand, some innovative clinical approaches are apparent which might be worth consideration, though not without more detailed study and information: 'Intestinal infections treated with lysozyme', 'Oestrogens . . . and vesico-ureteric reflux in children'. The English summaries as provided are, however, inadequate to assess the potential value of the work reported.

What advice can we give to our Soviet colleagues? What can we do ourselves to help the nation that produced Mechnikov and Pavlov make its full contribution to world paediatrics? Firstly, we should welcome them with open arms to visit and work in our departments and to attend our meetings, and we should encourage them to invite us back. Secondly, we should expect that if they are going to have the courtesy to include English summaries in their journal, the summaries should be precise, accurate, and quantitative; those in the *British Medical Journal* are an excellent example. And finally, if asked, we should surely be prepared to put in place a mechanism for linguistic and editorial assistance to make sure that those elements of the journal that are in English are clearly expressed in the language and answer the questions of a summary reader. 'Is there information in this article that I should consider applying to my practice or my research?' 'Is this an article I must get translated?' At present the answer is 'no' to both these questions for all the articles in the issues I read. With help—and should the editorial office of the *Archives of Disease in Childhood* pre-emptively offer such help?—we might hope to see the journal evolve into becoming a fully fledged partner in international paediatrics.

R H D BOYD

LETTERS TO THE EDITOR

Contractural arachnodactyly versus Marfan's syndrome

SIR,—I read with interest the case report by Huggon *et al* of an infant girl with contractual rachnodactyly, mitral regurgitation, and ridodonesis.[1] I agree that the presence of cardiovascular complications and iridodonesis obscures the differentiation between Marfan's yndrome and contractural arachnodactyly. However, there was no dilatation of the aortic oot reported in their patient.

The most characteristic cardiovascular bnormality in Marfan's syndrome is aortic oot dilatation.[2] Of all the cases of contractural rachnodactyly reported and cited as refernces by Huggon *et al*,[1] none had dilated ortic root. The only case quoted by the uthors that had enlarged aortic root was iagnosed as having Marfan's syndrome with ontractural arachnodactyly and severe mitral egurgitation.[3]

Although mitral valve prolapse has been ound in association with Marfan's synrome,[4] the major cardiovascular lesion assoiated with this syndrome is dilatation of the oot of the ascending aorta.[2] The latter is such frequent (84%) finding,[2] far more than itral valve prolapse (58%),[2] that in its bsence one should seriously question the iagnosis of Marfan's syndrome.

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Growth failure secondary to moyamoya syndrome

SIR,—The case report by MacKenzie *et al*, which describes a 7 year old boy with growth failure secondary to moyamoya syndrome is interesting.[1] We would like to draw your readers' attention to a highly specific electroencephalographic finding in childhood moyamoya syndrome. This finding makes it possible to establish the tentative diagnosis of moyamoya syndrome on the basis of electroencephalographic recordings alone in many instances.

With childhood moyamoya syndrome the electroencephalographic tracing will show the so called rebuild up phenomenon after the hyperventilation test. This phenomenon is characterised by a renewed prolonged high amplitude frequency decrease in the electroencephalographic tracing after the hyperventilation test. It occurs only in association with childhood moyamoya syndrome, and is probably dependent on the degree of vascular change.

Electroencephalographic findings of 87 children with moyamoya syndrome have been reported in the literature. Only four children, who suffered from stage V moyamoya syndrome, did not develop any rebuild up phenomenon after the hyperventilation test.[2–4] The rebuild up phenomenon might be attributed to increased vasoconstriction of the collateral vessels due to the induced decrease in oxygen, with delayed recovery after discontinuation of the hyperventilation test.

Our own finding of a rebuild up phenomenon in the electroencephalographic tracing, obtained in an 11 year old boy with no pertinent clinical symptoms, led us to establish the tentative diagnosis of a moyamoya syndrome which was confirmed by magnetic resonance imaging and angiography later.[5]

Regarding the patient described by MacKenzie *et al*, the moyamoya syndrome probably would have been diagnosed much earlier had the hyperventilation test been applied during the electroencephalographic recording and monitoring been continued sufficiently long. Due to the high specificity of the rebuild up phenomenon with regard to childhood moyamoya syndrome, we recommend magnetic resonance imaging or angiography whenever this electroencephalographic finding is obtained, even when clinical symptoms are absent. Only then will it be possible to extend proper advise to patients and parents.

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OCTOBER 1990 VOL 65 NO 10

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

1101 **James Spence Medallist 1990**

nnotations
1103 Diagnosis and management of subglottic stenosis after neonatal ventilation *M S C Morrissey, C M Bailey*
1105 Aplastic anaemia: continued cause for concern *David K H Webb*
1107 Audit—where do we go from here? *R I Ross Russell, P J Helms*

riginal articles
1109 Final height in boys with untreated constitutional delay in growth and puberty *E C Crowne, S M Shalet, W H B Wallace, et al*
1113 Short stature, mental retardation, and hypoparathyroidism: a new syndrome *R J Richardson, J M W Kirk*
1118 Hyperinsulinaemic hypoglycaemia in small for dates babies *J E Collins, J V Leonard, D Teale, et al*
1121 Treatment of chronic liver disease caused by 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase deficiency with chenodeoxycholic acid *H Ichimiya, H Nazer, T Gunasekaran, et al*
1125 X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis *G S Reusz, P F Hoyer, M Lucas, et al*
1129 Reappraisal of thyroxine treatment in primary hypothyroidism *S Hodges, B P O'Malley, B N Northover, et al*
1133 Survey of adolescents with severe intellectual handicap *J C Asthana, S Sinha, J S Haslam, et al*
1137 Normal small bowel biopsy followed by coeliac disease *M Mäki, K Holm, S Koskimies, et al*
1142 Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom *A Suzuki, E J Tizard, V Gooch, et al*
1147 Eight and 12 week courses of cyclophosphamide in nephrotic syndrome *N Ueda, K Kuno, S Ito*
1151 Continuous papaveretum infusion for the control of pain in painful sickling crisis *Patricia C E Sartori, Graham J Gordon, Philip J Darbyshire*
1154 Red cell membrane sodium transport: possible genetic role and use in identifying patients at risk of essential hypertension *J E Deal, V Shah, G Goodenough, et al*
1158 Predicting treatment outcome in nocturnal enuresis *J B Devlin, C O'Cathain*
1162 Capillary haemangioma presenting as a lung pseudocyst *J J Bowyer, M Sheppard*
1165 Benign intracranial hypertension after ciprofloxacin administration *A P Winrow, G Supramaniam*
1166 5 α-Reductase deficiency without hypospadias *W K Ng, N F Taylor, I A Hughes, et al*
1168 Indomethacin responsive hypercalcaemia associated with a renal sarcoma *J Gibbs, M J Dillon, S Lang, et al*

urrent topic
1170 Paediatric medical audit *R Primavesi, R MacFaul*

ersonal practice
1174 Management of migraine *Judith M Hockaday*

ersonal view
1177 Selective medical examinations for school entrants: the way forward *S Richman, M Miles*

1182 **Sister journals—Europe** *G McClure*
1183 **Letters to the editor**
1186 **Autumn books**
1192 **Current research themes**

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ARCHIVES OF
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The Journal of the British Paediatric Association

JAMES SPENCE MEDALLIST 1990

Professor Leonard B Strang

The James Spence Medal was presented to Professor Leonard Strang on 4 April 1990. Professor June Lloyd, President of the British Paediatric Association, gave the following citation:

Professor Leonard Strang

Leonard Strang is a true disciple of James Spence and it is typical of him that he would really have liked this citation to be an appreciation of that great man in whose honour we present this medal, our highest award. Leonard, however, cannot be allowed to escape an account of his own achievements; he has done so much in so many fields and my regret is that I shall not be able to do justice to all of them.

Leonard's clinical training started in Newcastle in the department established by Spence and in its early golden years. He very quickly showed his ability to observe the natural history of disease at the cotside, to apply physiological principles to the investigation of disease states, and to exploit basic science in the unravelling of clinical problems. These skills have been the cornerstones of his research career, which began with the development of respiratory function measurements in normal children and those with asthma, and progressed to systematic studies of the development and function of the lung in the perinatal period. After a spell at the Hammersmith Hospital where he held a Medical Research Council Fellowship and developed, among other things, techniques for the measurement of alveolar ventilation in the newborn, he had the opportunity to spend some time in the USA at Harvard where he concentrated on the changes in the pulmonary circulation. He subsequently continued this work in Oxford with Geoffrey Dawes, himself a James Spence medalist in 1969. Back in London Leonard soon moved to University College where he developed his systematic studies with series of elegant experiments on lung liquid, its production, control, and resorption. For this work he and his colleagues are internationally known and the proceedings of every workshop, symposium, or conference on the perinatal lung contain more entries under his name than almost any other. In 1976 he gave the Charles West lecture at the Royal College of Physicians of London and the Croonian lecture at the College in 1982.

But Leonard's contributions to paediatrics have extended far beyond the research environment be that laboratory, uterus, or neonatal nursery. He held the first chair of paediatrics in an undergraduate medical school in London and rapidly ensured that University College Hospital became a leading institution for paediatric education and research in that university. Just as his research work was systematic so was the way in which he recruited and nurtured younger colleagues. He took endless pains to see that each member of his staff was placed in jobs suitable for their talents and given the opportunity to turn their early 'geese like waddles' into the 'flight of swans'. It is no accident that six current holders of chairs in the UK have passed through his hands at a critical period in their careers—to say nothing of the innumerable consultants he has trained. His interest in training, however, extended more widely than simply among his own staff. He was concerned that the examination hurdle of the membership should be appropriate for, as he put it, 'the internal medicine of childhood' and, while Secretary of the Paediatric Committee of the Royal College of Physicians of London he helped push through the Paediatric Part II.

Academics are supposed to show excellence in research, in teaching, and in clinical care. Few manage to both achieve this tripartite feat and to sustain it throughout their careers. Leonard has been one of the few. His meticulous attention to the problems and needs of individual patients and their families is legendary; nothing was too much trouble, no hour of the day or night inconvenient, his patience with distressed and anxious parents was inexhaustible. Not so, however, was his patience with what he perceived as inattention, laziness, or just plain stupidity in colleagues or assistants. To those his explosiveness was equally legendary, even consultant colleagues have been known to come—or go—running.

Leonard has done much to raise the profile of British paediatrics in other countries. Nowhere has this been more apparent than in France. He is a confirmed Francophile and a perfect linguist. None of his friends were surprised—though they were probably saddened—when he chose to retire to France. We are delighted that he has recrossed the Channel to be with us today.

The James Spence Medal is awarded for outstanding contributions to the advancement or clarification of paediatric knowledge. Leonard has achieved both these things and it is a great pleasure to present him with the James Spence Medal for 1990.

James Spence Medallists

1960 Professor A A Moncrieff
1961 Professor R A McCance
1963 Sir F Macfarlane Burnet
1964 Professor L S Penrose
1965 Dr Cicely D Williams
1967 Professor R R A Coombs
1968 Dr Mary Sheridan
     Dr D W Winnicott
1969 Dr G S Dawes
1970 Professor D V Hubble
1971 Dr W W Payne
1972 Dr R C MacKeith
1973 Professor C A Clarke
1974 Dr J Bowlby
1976 Dr D M T Gairdner
1977 Professor R S Illingworth
1978 Professor S D M Court
1979 Professor K W Cross
1980 Professor J M Tanner
1981 Dr Elsie M Widdowson
1982 Dr D MacCarthy
1983 Professor J O Forfar
1984 Dr J W B Douglas
1985 Dr N S Gordon
1986 Sir Peter Tizard
1987 Professor J L Emery
     Dr F J W Miller
1988 Professor O H Wolff
1989 Professor D C Morley

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Annotations

Diagnosis and management of subglottic stenosis after neonatal ventilation

Acquired subglottic stenosis may occur after any intubation but is commonest after intubation in premature neonates in whom the incidence is between 1%[1 2] and 8%.[3 4] Recent recognition of the problem has led to more careful management of endotracheal tubes. It is now known that multiple intubations, tight fitting tubes with no air leak, excessive tube movement, and prolonged intubation all predispose to the development of stenosis.[5] The use of a nasotracheal tube fixed to the forehead with a Tunstall connector minimises movement. The Cole pattern tube has a shoulder which tends to wedge in the subglottis and cause stenosis,[6] and should be used for resuscitation only: a parallel sided tube should be used if intubation is to be continued.

Diagnosis

HISTORY

A child with subglottic stenosis after intubation may present with failure of extubation, stridor, recurrent 'croup', or reduced exercise tolerance. A hoarse voice or cry may be noted if scarring has involved the vocal cords. A history of previous intubations with special reference to the problems mentioned above must of course be sought.

PHYSICAL EXAMINATION

In stridulous patients assessment of the adequacy of the airway is paramount. Increased inspiratory effort with use of accessory muscles increases negative intrathoracic pressure leading to tracheal tug, intercostal, subcostal, and sternal recession. Some information can be gained from the demeanour of the child: lack of spare energy for playing or talking is significant.

Increased respiratory and pulse rates are common in these situations but cyanosis and bradycardia are ominous signs of decompensation.

Stridor in subglottic stenosis is inspiratory but may become biphasic as obstruction worsens.

SPECIAL INVESTIGATIONS

Radiographs should include a lateral soft tissue view of the neck, a posterior-anterior view of the chest, a high kilovolt coned tracheal ('Cincinnati') view, and a barium swallow.

All patients with appreciable stridor require microlaryngoscopy and bronchoscopy to assess the state of the larynx and the severity of the stenosis.

The size of the subglottis is measured using the bronchoscope[7] (a normal neonatal subglottis should have a diameter of 5·0 mm and admit a size 3·0 Storz ventilating bronchoscope).

An accurate assessment demands optimum anaesthetic conditions. Secretions are reduced by atropine premedication and the larynx is sprayed with a metered dose of lignocaine to prevent laryngospasm during instrumentation.[8] Spontaneous respiration is maintained throughout the examination, using an anaesthetic mixture of halothane and oxygen, with careful monitoring to avoid hypoxia.[9]

Treatment

If an infant has an airway that is inadequate there are two ways of approaching the problem. The traditional approach is to perform a tracheostomy and assess the child's airway every three months to decide whether reconstructive surgery is needed as the child grows. This has the advantage of getting the child back to a normal life as quickly as possible but carries an associated mortality of up to 10%[10 11]: the day to day management of a tracheostomy can be difficult for parents, and for some children speech development is delayed.

The second option is to perform a cricoid split. There are several modifications of this procedure but the basic principles are the same.[12] Under general anaesthesia the anterior lamina of the cricoid is divided and the edges distracted to enlarge the subglottic lumen. Some surgeons also split the posterior lamina and may even make lateral cuts in the cricoid. The endotracheal tube is then changed, on the operating table, for the largest size possible (usually a size 3·5 Portex). This tube stays in for 10 days while the child is paralysed and ventilated. Intravenous steroids are given for the final 24 hours and extubation is attempted. The operation can be repeated if necessary. The advantage is avoidance of a tracheostomy in approximately 75% of cases,[13] but it does require use of intensive care facilities for a prolonged period of ventilation.

If a tracheostomy has been performed then sizing of the subglottis at intervals will decide whether reconstructive surgery is required.[7] As a 'rule of thumb' a subglottic diameter more than one bronchoscope size too small for the age of the child will require surgical widening. In the absence of a tracheostomy then a decision about surgery will be based more on severity of symptoms.

The operation of choice for acquired subglottic stenosis is the laryngotracheal reconstruction[14 15] using an autologous costal cartilage graft.[16] Ideally this is performed at about the age of 2 years or when the child reaches 10 kg in weight.

Laryngotracheal reconstruction is performed through a separate incision above the tracheostomy at the level of the cricoid: the larynx is exposed from hyoid above to tracheostome below. The lumen is entered above the superior thyroid notch and the larynx is incised strictly in the midline to below the cricoid cartilage, through the stenotic segment. According to the severity and the distribution of the stenosis, an anterior and/or posterior graft is inserted to widen the cricoid ring. The graft is taken from a section of the eighth costal cartilage and sutured into place. A Silastic stent[17] is used to prevent the graft prolapsing and this is removed endoscopically after approximately eight to 12 weeks. During closure of the laryngofissure incision it is vital to appose the anterior commissure accurately or serious voice disturbance will result.[18]

Once the subglottis is seen to be healed with a good airway decannulation under hospital supervision can be attempted.[19] This usually occurs three to six months after surgery, and is successful in over 80% of cases.[7]

Complications of the operation include pneumothorax from the graft harvesting, and difficulty in swallowing which is usually temporary. Aspiration of food may occur if the Silastic roll is too high in the larynx in which case the stent is trimmed endoscopically. Late complications such as poor voice quality can occur,[11 20] especially if the graft is too high causing blunting of the anterior commissure or if the larynx is not closed correctly. Failure of the operation due to fibrosis or graft prolapse may require revision surgery.

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Aplastic anaemia: continued cause for concern

Aplastic anaemia is a rare disorder of haemopoiesis characterised by blood pancytopenia and bone marrow hypoplasia, with an overall incidence in the general population of 3–6 per million, and affecting 2–4 per million children under 15 years.[1–3] The age distribution is bimodal with peaks under 20 and over 40 years, and the incidence is higher in the Orient than the West,[4] probably reflecting greater exposure to environmental toxins and hepatitis. In most series there is a male preponderance.

Aetiology

The failure of haemopoiesis may be constitutional or acquired. Viruses (particularly non-A, non-B hepatitis and Epstein-Barr), drugs (chloramphenicol, non-steroidal anti-inflammatories, gold), and environmental toxins have been implicated but over 70% of acquired cases are idiopathic.[5] The mechanism of bone marrow failure is unclear in most cases. Haemopoietic precursors from index patients grow poorly in culture, and data for an immune mediated disorder are conflicting,[6–8] although a proportion of patients respond to immune suppression. In several series, up to 50% of adults treated with immune suppression by antilymphocyte globulin have subsequently developed a clonal disorder of haemopoiesis including acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria or myelodysplasia, and this argues for an underlying defect in haemopoiesis in many cases,[9 10] with viruses or drugs possibly acting as a 'trigger' in already abnormal marrow.

Constitutional causes of aplastic anaemia include Fanconi's anaemia (autosomal recessive trait, low birth weight, poor growth, and skeletal, cardiac, and urogenital anomalies) and dyskeratosis congenita (sex linked, nail atrophy, mucosal leucoplasia), and although Shwachman's syndrome is typified by neutropenia and exocrine dysfunction of the pancreas, pancytopenia occurs in a minority of children.

Diagnosis

At diagnosis, the history should include specific inquiry regarding drug exposure, possible toxins, and recent infections, particularly hepatitis. Examination may reveal stigmata of Fanconi's anaemia or dyskeratosis congenita. The blood film shows a variable degree of pancytopenia, and one or more cell lines may be disproportionately affected. Although pallor and bruising are usual at presentation, infection and haemorrhage are less common, and indicate a poor prognosis.[11] A trephine biopsy to assess marrow cellularity is essential, and typically shows pronounced hypocellularity with replacement of haemopoietic tissue by fat cells. Marrow involvement may be patchy with residual islands of normal or increased cellularity, which may cause diagnostic uncertainty. Inflammatory cells may be prominent, and residual haemopoietic cells may be mildly dysplastic, but there is no increase in blasts and malignant cells are not seen.

Initial investigation should exclude constitutional causes of marrow failure. In Fanconi's anaemia culture of blood lymphocytes with diepoxybutane or mitomycin C reveals an increase in chromosomal breaks, gaps, rings, and translocations, a manifestation of the underlying defect of DNA repair in this disorder. Imaging may show skeletal, cardiac, or renal abnormalities. A Ham's (acidified serum lysis) test is required to exclude paroxysmal nocturnal haemoglobinuria, a disorder of haemopoiesis characterised by increased sensitivity of erythrocytes to lysis by complement, which may precede or evolve from aplastic anaemia. Viral serology and liver function tests may show evidence of hepatitis, Epstein-Barr virus, or parvovirus infection.

Disease severity is assessed by the modified criteria of Camitta *et al* (table),[12] which primarily reflect the severity of blood pancytopenia and have considerable prognostic importance. Patients with $<0\cdot2\times10^{9}$/l neutrophils fare particularly poorly and are identified as having very severe aplastic anaemia, whereas more mildly affected individuals have non-severe aplasia.

Treatment

Children with severe aplastic anaemia have a poor prognosis with supportive care alone, with only 20% surviving one year from diagnosis.[13] Broad spectrum antibiotics are essential for infections, with blood and platelet transfusions as clinically indicated, and blood products should be leucocyte depleted to reduce sensitisation to HLA antigens; this is most conveniently achieved by in line filters at the bedside. Refractoriness to platelet transfusion develops in 50% of those who have had several transfusions, but is not dose dependent, and prophylactic platelet support may be indicated in severe cases.[14 15] Ideally patients with negative serology for cytomegalovirus should receive cytomegalovirus negative blood products, but the use of leucocyte depleting filters may reduce the risk of its transmission from unscreened blood products.[16]

In acquired aplastic anaemia, the options for curative treatment lie between allogeneic bone marrow transplantation for those with an HLA full match family donor, and immune suppressive treatment. Children with severe or very severe aplastic anaemia are best treated by bone marrow transplantation, and recent experience indicates an 80% five year disease free survival in such cases.[13 17] Graft rejection, once a major barrier to success, has been reduced by modern preparative schedules incorporating cyclophosphamide and cyclosporin,[18] and graft versus host disease is generally mild and responsive to treatment in paediatric series. Similarly, infection with cytomegalovirus, a major cause of death in adult transplants, is a less common complication of bone marrow transplantation in childhood. Survival is improved by early compared with delayed transplantation,[19] and all families should be tissue typed at presentation. Unfortunately, 70% of patients have no family donor, and treatment for these cases is by immune suppression in the first instance.

Antilymphocyte globulin (or antithymocyte globulin) is the standard method of immune suppression in aplastic anaemia, and is administered as a five day course via a

Criteria for severe aplastic anaemia[12]

Blood (at least two of three must be present):
(1) Neutrophils $<0\cdot5\times10^{9}$/l
(2) Platelets $<20\times10^{9}$/l
(3) Corrected reticulocytes <1%

Bone marrow:
Either: cellularity <25% normal
Or: cellularity ≤50% normal, with residual haemopoietic cells <30%

central venous catheter. A test dose is necessary as a precaution against anaphylaxis, platelet transfusion is indicated because antilymphocyte globulin exacerbates thrombocytopenia, and methylprednisolone cover is necessary to reduce the otherwise high incidence of serum sickness. The response to antilymphocyte globulin may be delayed, and observation for three to four months is necessary to detect improvement. A second course may prove effective if the initial response is unsatisfactory. The overall response rate is 50–60%, and is greater in non-severe compared with severe aplastic anaemia, but in many cases antilymphocyte globulin results in improvement rather than normalisation of the blood count.[20] An unsatisfactory response to antilymphocyte globulin is most likely in patients with a neutrophil count of $<0{\cdot}2\times10^9$/l, sepsis, or haemorrhage, in young children, and females.[19] In the few paediatric series survival rates have ranged from 40–70%,[13 21] but patient numbers were small, and follow up short.[21] Subsequent relapse of aplastic anaemia occurs in 30% of cases.[22] Several series have described the evolution of acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria, or myelodysplasia in 30–50% adults treated with antilymphocyte globulin, although these complications have not been described in children. These reservations notwithstanding, at present antilymphocyte globulin remains the treatment of choice for cases with non-severe aplastic anaemia. Although of no proved benefit when used alone, androgens may be synergistic in combination with antilymphocyte globulin, and controlled studies are underway to resolve this question.

For patients who have failed first line treatment, responses have been described after immune suppression with cyclosporin or high doses of methylprednisolone.[23 24] Of these cyclosporin is the more promising, and has proved useful in patients who have relapsed after or failed to respond to antilymphocyte globulin. Controlled studies of cyclosporin alone and in combination with antilymphocyte globulin are in progress. Improvements in neutrophil counts during treatment with the recombinant haemopoietic growth factor granulocyte macrophage colony stimulating factor are of interest, but this treatment had no effect in patients with very low neutrophil counts, or sepsis at the time of treatment.[25 26] Finally some patients have received transplants from matched unrelated donors, or family donors with some degree of mismatch, and although this approach is experimental[27 28] it may offer the best hope of cure for patients unresponsive to first line treatment.

The pancytopenia of Fanconi's anaemia responds to oral androgens, but an increased risk of leukaemia in these children and the potential toxicity of androgen treatment indicate bone marrow transplantation as the treatment of choice whenever possible. Due to the defect in DNA repair, these children are particularly sensitive to standard preparative regimes, but good results are now obtained with reduced dose treatment.[29] Treatment for dyskeratosis congenita is unsatisfactory as there is an increased risk of epithelial neoplasia in these patients.

In conclusion, despite progress in the management of aplastic anaemia, this condition remains a major challenge for the future. Accurate dignosis, early referral, and support with antibiotics and blood products as indicated remain essential to maximise the prognosis for children affected by this often devastating disease.

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Audit—where do we go from here?

What is audit?

Although in common use, the term medical audit is poorly understood, and can mean different things to different people. Formally, it constitutes a discipline incorporating a cyclical process of evaluation, improvement, and re-evaluation. Evaluation in this context is defined by the World Health Organisation (WHO) as 'the systematic and scientific process of determining the extent to which an action or set of actions was successful in the achievement of predetermined objectives'.[1] Most clinicians would claim that the critical evaluation of the quality of their work is something they have always taken an interest in. For the majority, this would include reviews of their clinical practice in the light of current medical literature, attendance at postgraduate courses, and regular meetings with colleagues, such as occurs in the presentation of cases at regular clinical meetings. Although such forms of review are helpful and may lead to improvements in clinical practice, they do not fulfil the more rigorous requirements of formal medical audit,[1] which requires that the objectives are clearly stated before audit begins, and that any changes in policy can be implemented and monitored.

The WHO definition clearly requires refinement. Firstly, 'predetermined objectives' must be established by an acceptable body of opinion. Secondly, those taking part must be prepared to review critically their work and make appropriate changes to their practice. Thirdly, there must be some form of continuing review to ensure that the agreed changes are maintained. From the above it becomes clear that the only possible approach to quality review in medicine is peer review.[2] Yet while accepting the need for quality control to be governed by clinicians, it is appreciated that different interest groups, such as health care economists, health care professionals, politicians, and patients, will have different understandings as to the meaning of quality of care. These differing views must be taken into account by clinicians developing standards for measuring quality of care. It is also recognised that most existing measurements of quality of care are crude,[3,4] and there is a real danger that what can be easily measured will be used to draw inappropriate conclusions. What is needed is the laborious but important task of developing more robust measures than are currently available. These should have a high level of consensus among health care professionals as well as being understood by and acceptable to the consumers of health care, namely our patients and their families.

Systematic approaches

So if our current measures of quality of care are crude, can they be improved? The first step in such a process must be clearly to define the components of the activities involved.[5–7] Some type of analysis of the activities under review must be carried out before audit can sensibly be applied. In the commercial world, and in particular in the area of industrial production, the three broad headings that are analysed and quality assured are: (i) raw materials and supply, plant, and personnel, (ii) the production processes themselves, and (iii) the final product.[5] These concepts have also been applied to health care. Donabedian in particular has analysed the elements of health care, and uses the terms structure, process, and outcome.[5,6] This is the approach recommended in the recent white paper[8] and by the Royal College of Physicians own report.[1] Yet there is some doubt as to how far this approach, taken from the world of industry and commerce, is appropriate in a 'business' driven by health needs and expectations.

'Resource management' techniques have a major role in activities such as estate and capital planning, personnel, and supplies, but their introduction into the assessment of quality of care without further modification may not be appropriate. There is among many health care professionals a considerable unease about the appropriateness of applying an industrial model of audit and resource management to the interaction between carer and patient, and the increasing use of 'performance factors' to represent what is an extremely complex process.[1,9]

Against this background, professional bodies representing medical opinion in the UK have sought to strengthen and extend medical audit by producing guidelines for its introduction and conduct.[1,10,11] In these recommendations the three major headings outlined above have been maintained, namely structure (or resource), process, and outcome audit. While such headings can be helpful, there is a great deal of overlap between them. The interrelationships between resources and process, or process and outcome, must be carefully explored. Only when these complex relationships are described and properly understood, can valid measurements be derived and used to assess the quality of the service.[5]

Resource

Resource audit is relatively easy to understand and to define. It includes the analysis of all resources that are required for the health care process under review, and their comparison with agreed standards. These resources include staff numbers, level of training and experience, the physical environment where the process is carried out, equipment, laboratory and investigative facilities, and available treatments.[5] The organisation and conduct of audit itself should also be included under this broad heading. Resource audit is an area in which business style resource management can be applied with some success.[12]

Outcome

Outcome audit has been more difficult to define. While the need for, and the value of, measuring output is undisputed, the most difficult aspect of such audit is the definition of appropriate measures of outcome. Most commonly used is mortality,[13,14] but this is very crude and presents obvious difficulties in diseases with very low mortality.[4] The assessment of outcome after neonatal intensive care is an example where further development is required. Crude mortality figures (for example, survival to discharge) give no indication of morbidity. The inclusion of data on long term handicap and other measures of morbidity, can result in very different conclusions.[15] Measures such as subsequent morbidity, handicap, and quality of life, however, are not easy to define and are consequently less amenable to critical analysis than mortality. Such measures are, however, being developed and refined.

Measures of quality of life have been developed for adults,[9] [16] but few are so far available for children. Questions about perceived quality of life, patient satisfaction, and physical functions allow the construction of a comparative hierarchy against which outcome can be assessed.[5] Such methods, however, have major difficulties when applied to a paediatric population in which functional outcome is difficult to measure.

One fundamental requirement of outcome audit is its reproducibility both between and within observers. This need for reproducibility also restricts the use of descriptive measures of outcome. Even objective data such as mortality can be subject to criticism if confounding variables are not accounted for. Recent work demonstrating that mortality in cystic fibrosis is lower in groups of patients seen in specialist regional centres,[17] has been criticised as being confounded by variations in social class between the groups cared for locally and at regional centres.[18]

Process

The most difficult, and consequently most poorly defined area of care is that of the process of health care itself. The current application of audit to this area, at least as far as hospital medicine is concerned, is almost entirely based on reviews of case notes. Reviews of diagnoses or management decisions are based on the retrospective interpretation of the notes, rather than prospective assessment of the physicians' performance. Such prospective assessments are not made because the appropriate measures have not been clearly defined. This is hardly surprising as verifiable and meaningful measures cannot be produced until the clinical process itself has been analysed and defined. Most of the early attempts at such analysis—that is, the detailed description of those activities that are involved in health care—have been undertaken by the nursing profession. Work by Henderson, Orem, and Roper has had a great impact on the nursing approach to health care by attempting to define the role of the nurse and by describing the nursing process in a systematic way.[19–21] Severity scoring systems may also have a place in measuring the process of health care.[4] [22] These have developed measures of illness severity and treatments given to allow a prognosis to be given for a patient. Although they have generally been used to measure outcome, their adaptation may provide a useful measure of interventions that occur in clinical practice,[12] and this could be used to evaluate the care given to any particular patient.

Analysis has only very recently been applied to the medical aspects of health care. This is partly due to the complexity of the subject, but also reflects a failure by many clinicians to understand the importance of a systematic analysis of their activities. No clinician in this age would accept drug treatments that had not been subjected to rigorous safety checks and clinical trials. Yet we are often far less rigorous assessing other aspects of care. For example, the management of a patient's fluid balance, the formulation of a care plan, or the analysis of a radiograph are the kind of activities that are based on personal experience coupled with established medical practice. As such they are consequently difficult to analyse as they may be idiosyncratic and unique to a particular group, or to an individual clinician. Analysis of the process of medical care is needed so that agreed measures can be established and valid comparisons made between different disease states and managements. Such modelling should not enforce a 'standard approach' but rather identify the components of the clinical process which are held in common across a wide range of disease states and medical management styles.

Conclusion

The term audit can mean different things to different people, and therefore its objectives and conduct must be agreed between all parties involved before it is established. It has great importance to practising clinicians, who have an obligation to review critically and maintain the quality of the service they provide. Whether we like it or not, we are all going to become involved in the systematic audit of our work. However, we must continue to develop scientifically sound measures of health care that truthfully reflect the work carried out. With the financial pressure that is being increasingly put on clinicians to justify the escalating cost of health care, there is a real risk that purely economic considerations may be used to apportion funding, which may be to the detriment of the quality of care we can provide. To avoid this we must demonstrate the relationship between quality and quantity of care. The way ahead must be to learn from the experience of systematic clinical audit (with all its limitations), to continue careful and thorough analysis of all the processes of health care, and to develop reliable and reproducible measures of outcome.

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ORIGINAL ARTICLES

Final height in boys with untreated constitutional delay in growth and puberty

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Abstract

To determine the natural history and psychological impact of the growth pattern in boys with constitutional delay in growth and puberty (CDGP), 43 boys presenting with short stature due to CDGP were followed up to final height. At presentation mean (SD) chronological age was 14·0 (1·9) years, bone age delay 2·7 (1·0) years, standing height standard deviation score (SDS) −3·4 (0·6), and predicted adult height SDS −1·3 (0·7). Final adult height SDS was −1·6 (0·9), measured at 21·2 (2·6) years. There was no significant difference between final height and predicted adult height, but there was a significant difference between final height and measured mid-parental height.

Psychological questionnaires showed no significant difference in self esteem, marital, or employment state between the CDGP group and a control group. There was no correlation between self esteem and final height, but 25 felt their growth delay had affected their success either at school, work, or socially and 20 would rather have had treatment to advance their growth spurt.

This study supports the more frequent use of active medical treatment to advance growth in boys with CDGP, and shows that although boys with CDGP reach their predicted heights, this is short for their families.

Short stature due to constitutional delay in growth and puberty (CDGP) is commonly seen in paediatric practice, and although an extreme of normal development rather than a clinical disorder, can still pose considerable clinical problems. There is a significant number of patients who remain unhappy despite explanation of the diagnosis and promise of normal growth to come and eventual normal final adult height when growth is finished. In this group psychological distress may affect behaviour and school performance and according to some authors persists into adult life.[1–3] Hence the use of pharmacological treatments to improve short term growth and allow the patients, usually adolescent boys, to keep pace with their peers.[4–8] Assessment of growth and psychological responses to treatments such as low dose testosterone, oxandrolone, and especially growth hormone requires knowledge of the natural history and outcome of untreated CDGP. We have therefore reviewed the growth and psychological wellbeing of boys with CDGP seen in growth and endocrine clinics between 1976 and 1986 who did not receive hormonal treatment and who have now reached their final height.

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Patients and methods

The records of 118 boys seen between 1976 and 1986 with short stature due to CDGP were reviewed. The boys had all had CDGP diagnosed when first seen. Five had attended clinic until reaching their final height. The remaining 113 were contacted by letter: 38 replied and agreed to come back to clinic, two refused to return, 15 letters were returned as the families had moved, and 58 remained unanswered. The 38 responders returned to clinic for measurement and to complete a psychological questionnaire. The 43 patients followed up to final adult height fulfilled the following criteria at presentation:

(1) Short stature (height less than 2 SD below the mean).

(2) Delayed puberty (onset delayed by more than 2 SD—that is, had not achieved 4 ml testes until aged 14 years).

(3) Bone age below the 10th centile for chronological age (delayed by more than 1·5 years).

(4) No clinical evidence of chronic disease or endocrinopathy.

They were considered to be at their final adult height if growing less than 2 cm/year or aged more than 21 years. All had completed normal pubertal development. Standing and sitting height measurements were performed using a fixed Harpenden stadiometer and subischial leg length was obtained by subtracting sitting height from standing height. Standard deviation scores (SDS) were calculated using published tables.[9] Pubertal stage was assessed according to the method of Tanner and Whitehouse.[10]

Chronological age, height, and pubertal stage at presentation were obtained from the notes both of those measured to final height (group A) and a randomly selected sample of those whom we had not traced (group B, n=33) in order to ensure that those who responded positively were truly representative of the whole cohort of boys with CDGP. The bone ages were assessed according to the method of Tanner and Whitehouse by one observer (ECC) and predicted adult height estimated using the Tanner-Whitehouse II method.[11] Mid-parental height was obtained using reported parental heights (the mean of father's height and mother's height plus 12·5 cm). Target genetic height is defined as the mid-parental height±8·5 cm and represents the range of heights likely to be achieved by 95% of a couple's sons. In a subset (n=40) parental heights were checked using a portable microtoise stadiometer.

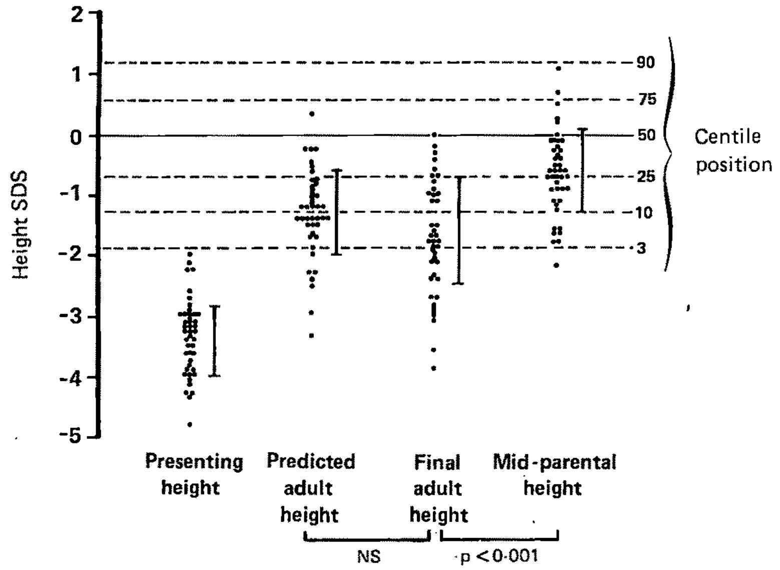
To assess self esteem and social function, questionnaires were administered. These consisted of the adult Coopersmith self esteem inventory,[12] and a questionnaire asking specifically about current attitudes to height, current social and employment history, what problems, if any, they attributed to their growth delay and, if in retrospect they would rather have had treatment. The results of these questionnaires were compared with those of a group of 43 normal young men of the same age range and living in the same area who were drawn from hospital employees and their families. This group was chosen rather than a student population as being more comparable in social activity. There was no significant difference in social class between the control and study group but the groups were not matched for height, the control group being significantly taller (height SDS 0·47 (1·05) (reported height) compared with −1·6 (0·9), $p<0·001$).

Table 1 Growth data at presentation of boys with CDGP. Results are mean (SD)

Data at presentation	*Group A (n=43)*	*Group B (n=33)*
Age (years)	14·0 (1·9)	14·1 (1·9)
Bone age (years)	11·3 (2·5)	11·4 (2·1)
Bone age delay (years)	2·7 (1·0)	2·8 (0·8)
Standing height (cm)	139·0 (11·4)	141·6 (10·4)
Standing height SDS	−3·4 (0·6)	−3·0 (0·9)
Mid-parental height (cm)	170·6 (4·8)	171·5 (5·9)
Mid-parental height SDS	−0·6 (0·7)	−0·5 (0·9)
Predicted adult height (cm)	166·1 (4·6)	167·2 (3·9)
Predicted adult height SDS	−1·3 (0·7)	−1·2 (0·5)

Table 2 Data at final height of 43 boys with CDGP. Results are mean (SD)

Data at final adult height	
Age (years)	21·2 (2·6)
Standing height (cm)	164·1 (6·0)
Standing height SDS	−1·6 (0·9)
Sitting height (cm)	87·8 (3·1)
Sitting height SDS	−1·7 (1·0)
Leg length (cm)	76·1 (3·9)
Leg length SDS	−1·2 (0·9)
Leg length SDS minus sitting height SDS	0·5 (0·9)
Change in height SDS	1·8 (0·8)
Final height minus predicted adult height (cm)	−2·0 (4·5)
Final height minus mid-parental height (cm)	−6·5 (6·0)



Presenting height, predicted adult height, final height, and mid-parental height SDS for 43 boys with constitutional delay in growth and puberty.

Results were expressed as mean (SD). Statistical analyses were performed using the Mann-Whitney U test and Student's paired and unpaired *t* test.

Results

Comparison of the data at presentation between groups A and B (table 1) shows no significant differences in chronological age, bone age delay, standing height, mid-parental height, or predicted adult height between those whom we were able to trace and follow up to final height and those who were lost to follow up.

GROUP A: GROWTH DATA

For those followed up to final height there was a significant improvement in height SDS (−3·4 (0·6) to −1·6 (0·9), $p<0·001$) (table 2). Final height was above the third centile in 32 (74%), and above the 10th centile in 20 (47%) (figure). There was no correlation between final height and social class.

(1) Comparison of final adult height and predicted adult height (figure)

There was no significant difference between final height and predicted adult height (SDS −1·6 (0·9) compared with −1·3 (0·7)). The mean difference was −2·00 (4·5) cm. In seven boys (16%), the final height was more than 5 cm below the predicted adult height, and in two (5%), more than 5 cm above the predicted adult height. There was no correlation between the accuracy of the height prediction and chronological age, height, or bone age at presentation but there was a significant correlation with bone age delay at presentation ($p<0·001$) so that the greater the bone age delay the less accurate the height prediction proved to be.

(2) Comparison of final adult height and mid-parental height (figure)

There was a significant difference between final height and mid-parental height ($p<0·001$), with a mean difference of −6·5 (6·0) cm. The reliability of reported heights is suspect, and in fact there was a significant difference between the reported and measured mid-parental heights (170·9 (4·9) compared with 168·3 (4·1), $p=0·03$). In 14 of the 20 sets of parents measured this difference was less than 1 cm. In the remaining six couples (32%) the difference was greater than 2·5 cm. Four couples overestimated and two couples underestimated their height. The difference between final height and measured mid-parental height was still significant in this subgroup ($p=0·003$).

(3) Comparison of sitting height and leg length

To look for disproportion, leg length SDS minus sitting height SDS was calculated and was within 2 SD of the mean in all cases. There was, however, a significant difference between leg length SDS and sitting height SDS ($p=0·03$), with a mean difference of 0·5 (0·9). There was

Table 3 Replies to psychological questionnaires

Question	*No (%) replying yes*	
	CDGP (n=38)	*Normals (n=43)*
Are you satisfied with your height?	30 (79)	42 (98)
Would you like to be a different height?	23 (60)	2 (5)
Do you think your height interfered with your success at school/work/socially/sports?	25 (65)	7 (16)
Did coming to the clinic make you feel better?	22 (57)	—
Did coming to the clinic make you grow better?	6 (15)	—
Would you rather have had treatment to make you grow sooner even if you ended up the same height?	20 (53)	—
If you had children with delay in their growth, would you want treatment to make them grow sooner?	21 (55)	—

no significant correlation between bone age delay at presentation and the difference between adult leg length SDS and sitting height SDS.

QUESTIONNAIRE MEASURES

There was no significant difference in self esteem, measured by the Coopersmith self esteem inventory, between the boys with CDGP and the normal group (77·6 (14·8) and 76·8 (12·9) respectively). Neither did they differ in social activity applying the scoring system used to assess their social lives. There was no significant correlation between their self esteem score and any of the following variables: social class, final adult height achieved, gain in height since presentation, bone age delay at presentation, and the shortfall between achieved adult height and either mid-parental height or predicted adult height. There was no significant correlation between self esteem and social activity.

There was no significant difference between the number married or in stable relationships between the two groups (35 in the CDGP group and 31 in the normals) or in the number unemployed (one and two respectively).

The replies to the questionnaire about attitudes to height are shown in table 3. Eighteen said they no longer thought about their height at all, a further 17 only occasionally. Thirty of the CDGP group were satisfied with their final height as compared with all but one of the normals, this despite the fact that the CDGP group were significantly shorter than the controls. A total of 23, however, did want to be a different height, that is, taller, compared with only two of the controls. Twenty five thought their height had interfered with success—in everything (n=3), socially (n=13), at school because of teasing (n=9), and in sport (n=9). Eight did not remember being worried themselves about their height. Attendance at a clinic had made 22 of the boys feel better and six thought it had made them grow better. Even though most were now happy about their height, 20 would rather have had treatment to bring forward their growth spurt and 21 wanted such treatment available for their children if faced with a similar growth problem.

Discussion

This study illustrates the difficulties inherent in following up boys with CDGP to final height, and may well account for the paucity of data on its untreated course. By the nature of the condition, the boys are not ill, have not received treatment, and once they have started their pubertal growth and development, not unnaturally, usually prefer to leave the clinic. This age group are also mobile geographically and can be difficult to trace retrospectively. Our sample, although only 37% of the full cohort, did not differ significantly from the remainder in any of their presenting features. There is therefore no obvious bias in selection and their growth pattern should be representative of the group as a whole.

The boys showed a significant improvement in height SDS, as expected in a condition where growth is merely delayed. The majority achieved their predicted height, although there was a significant number (21%) where the prediction differed by more than 5 cm. This is in agreement with recent reports of final height in smaller numbers of boys with untreated CDGP.[13 14] Our results indicate, however, that although most boys reach their target genetic height, as a group they are significantly shorter than their mid-parental heights. This was also shown by LaFranchi *et al*, although they used reported parental heights only.[13] We were able to measure a subset of parents, and although a significant difference between reported and measured heights was found, the sons were still significantly short in the context of their parental heights. These results need to be taken into consideration when assessing the need for active treatment, particularly in boys with short parents, but also when analysing the outcome of hormone or drug treatment on final height in boys with CDGP.

Although there was a significant difference between leg length SDS and sitting height SDS (mean 0·5 (0·9)) this does not mean there was a significant disproportion at final adult height. This discrepancy has also been noted in other groups of children in whom disproportion would not be expected,[15] and may simply reflect the difference in sitting height measurement using the Harpenden stadiometer as the original SDS tables were constructed using measurements from an anthropometer.

At present the principal reason for treating boys with CDGP with growth promoting agents is to alleviate the short term distress caused by the discrepancy in development in comparison with their peers. Poor achievement in education has been found to correlate with late maturation in boys in a study that controlled for intellectual abilities.[16] In addition, impressionistic studies indicate that the adverse psychological impact may persist into adult life.[3] We found no significant difference in self esteem, marital, or employment state between our study group and the controls. It must also be stressed that there are individual differences because of 'a complex interplay of factors' so that the response of any individual to late development will be modified by other physical, psychological, or social factors. Although these young men had normal self esteem and social functioning, 60% did want to be taller than their achieved final height. The majority (79%), however, were satisfied with their eventual height and no longer regarded it as a problem. Furthermore as there was no correlation between self esteem and final height achieved, this would argue against the need for treatment for the majority designed to actually improve final height.

On the other hand, the young men also recalled the difficulties their short stature had caused them. A half felt it had affected their success especially at school and socially. Furthermore, half felt that in retrospect they would have liked treatment to advance their growth spurt, and 55% wanted the availability of such treatment for any of their children faced with the same growth problem. These results support the notion of both hormonal and psychological intervention at the time of presentation to treat and prevent distress at that time.

In conclusion, therefore, our results demonstrate the expected improvement in growth rate in boys with CDGP, but suggest that they do not in fact achieve their full genetic potential. We did not demonstrate a link with poor self esteem or reduced social activity, but although the boys were past their growth problems, there was retrospective evidence of significant psychological distress in adolescence and a strong desire from the boys themselves for active treatment, although attendance at clinic had provided some reassurance. Remaining problems include the definition of criteria to be used in determining which boys with CDGP should be treated, and the development of suitable methods of assessment of the impact of such treatments on their psychological well being. Prospective randomised trails are necessary to address these points.

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Short stature, mental retardation, and hypoparathyroidism: a new syndrome

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Abstract

Eight children (four boys and four girls) with extreme failure to thrive, dysmorphic features, developmental delay, hypoparathyroidism, and abnormal skeletal survey were studied. They were the products of seven consanguinous marriages, two of the patients being brothers. In the remaining six families, a further four children had affected siblings who had died in infancy. When assessed the children were aged 0·47–12·8 years; SD scores were <−2 for height, weight, and head circumference in all patients. The children had identical facies with deep set eyes, depressed nasal bridge with beaked nose, long philtrum, thin upper lip, micrognathia, and large floppy earlobes. They were all developmentally retarded. The following abnormalities were found on investigation: hypocalcaemia in all (of whom six of seven had hypoparathyroidism), medullary stenosis and other skeletal survey defects in seven of the eight children, and reduced numbers of T cell subsets in four of four tested. We believe that these children represent a new, as yet undescribed genetically determined syndrome.

Table 1 Clinical features of the syndrome. All patients had consanguinous parents and were of short stature with developmental delay and typical dysmorphic facies

Case No	*Sex*	*Affected siblings*	*Low birth weight (<10th centile)*
1	Male	Yes	Yes
2	Male	Yes	Yes
3	Male	No	Yes
4	Male	Yes	Yes
5	Female	Yes	Yes
6	Female	No	Not known
7	Female	Yes	Yes
8	Female	Yes	Yes

During the past few years we have noted a previously undescribed pattern of congenital anomalies in eight children of Middle Eastern origin. We present these cases in the hope that early recognition may reduce morbidity and mortality from associated hypocalcaemia and sepsis, and enable further elucidation of the genetics of this syndrome.

The clinical features of the syndrome are summarised in table 1, and show clearly the homogeneity of the abnormalities in these children. We therefore describe the index case in

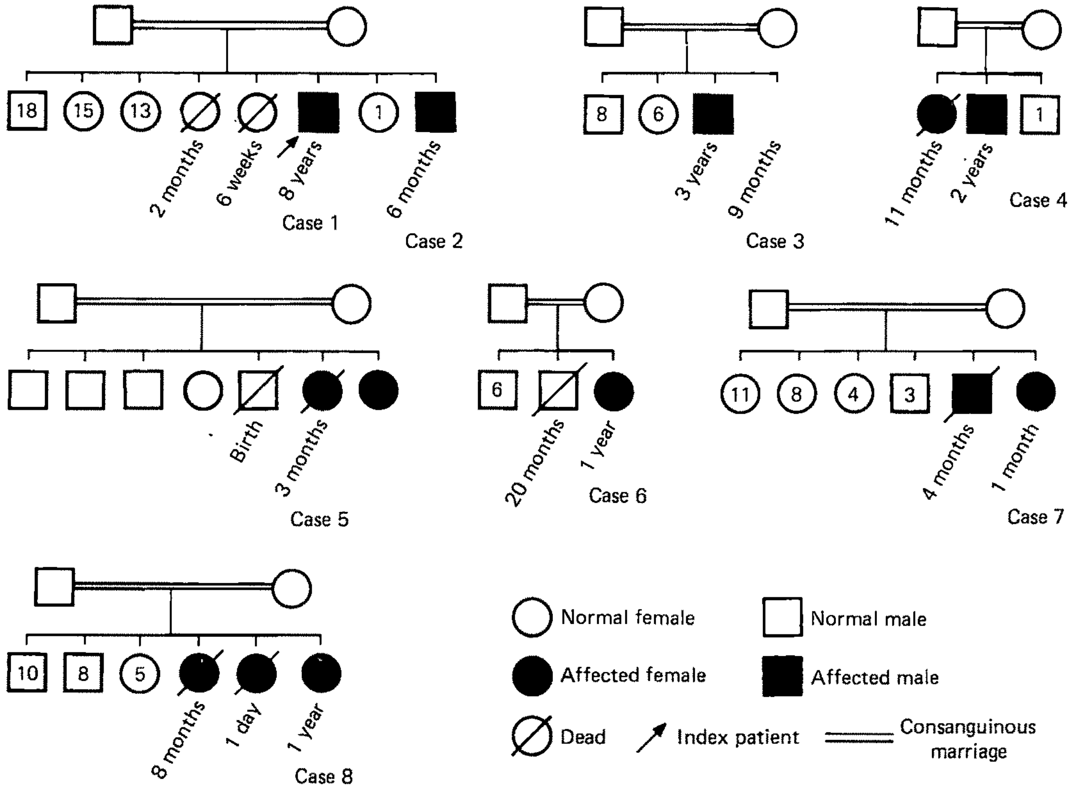

Figure 1 Pedigrees of affected families.

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detail, and then review the abnormalities in the other patients.

Case reports

CASE 1

This infant boy was the sixth liveborn child born to consanguinous first cousins from Qatar. He was the older brother of case 2. He also had a brother aged 18 years, and two sisters aged 15 and 13 years, but two other sisters had died in infancy (fig 1).

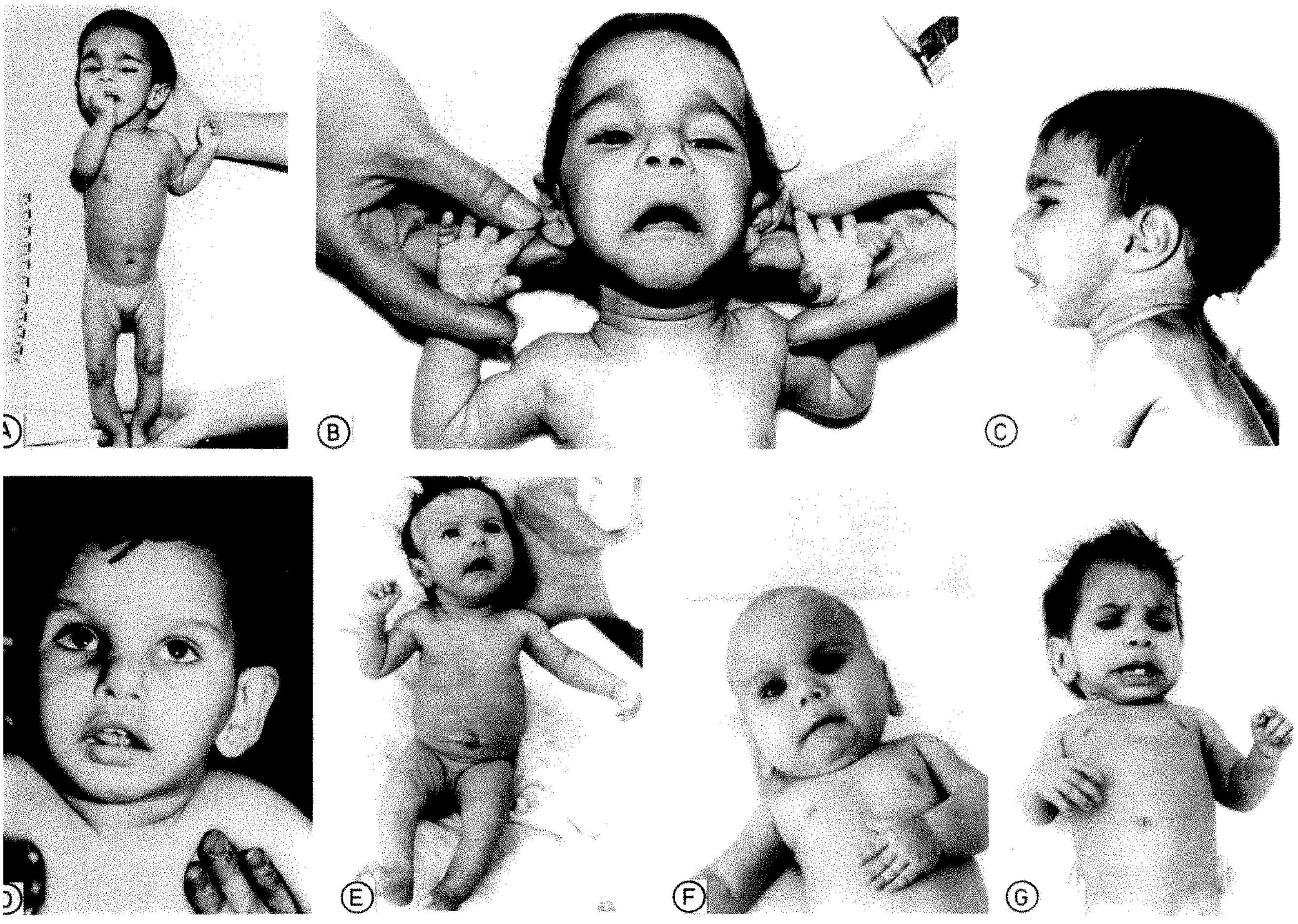
The pregnancy was normal, although low urinary oestriol concentrations had been noted. The baby was born in the United Kingdom at full term weighing 1840 g (table 2). At birth he was noted to have dysmorphic features—deep set eyes, a beaked nose with depressed nasal bridge, long philtrum with thin upper lip, micrognathia, and large floppy earlobes (fig 2). At 3 weeks of age he developed septicaemia and streptococci, staphylococci, coliforms, and candida were cultured. At that time he was found to be hypocalcaemic (calcium 1·5 mmol/l, reference range 2·20–2·67) with an inappropriately low parathyroid hormone concentration (<156 ng/l) (table 3). Treatment was started with 1α-hydroxycholecalciferol. He was also discovered to have β thalassaemia major, for which he required intermittent blood transfusions.

No syndrome or underlying cause was found for this child's condition, but despite treatment of both the thalassaemia and hypoparathyroidism he has remained severely developmentally and physically retarded. He started to walk at the age of 8 years and at that time speech was limited to babble and a few words, but no sentences. At the age of 12 years the vocabulary was still extremely limited, consisting only of simple phrases and sentences. Vision and hearing were normal.

Growth has been extremely poor (fig 3). When last reassessed at the age of 12·8 years his height was 81·9 cm with a weight of 9·0 kg

Table 2 Auxological data

Case No	Birth weight (g)	Gestation (weeks)	Centile (%)	Age (years)	Height		Weight		Head circumference	
					cm	SD score	kg	SD score	cm	SD score
1	1840	40	<3rd	12·81	81·9	−10·6	9·0	−3·6	45·0	−9·1
2	2150	36	<3rd	5·17	69·1	−8·4	7·0	−5·3	40·0	−8·7
3	2540	37	<10th	3·01	76·2	−4·7	7·2	−4·6	42·8	−4·0
4	1930	41	<3rd	1·91	61·2	−7·7	4·5	−5·8	39·4	−6·2
5	2700	40	<10th	1·47	61·5	−6·3	3·7	−6·6	40·2	−4·9
6	2320	39	<3rd	1·09	54·5	−7·6	3·5	−6·2	38·5	−5·3
7	Not known	Not known	Not known	0·09	46·5	−3·3	2·4	−2·9	33·0	−2·3
8	2360	38	<3rd	1·24	51·4	−9·2	2·9	−7·0	38·6	−5·5



igure 2 *Photographs of affected children. A, B, and C—index case aged 9 months; D, E, F, G—cases 3, 6, 7, and 8.*

Table 3 Calcium studies

Case No	*Calcium studies*			*Parathyroid hormone (ng/l)*
	Calcium (mmol/l)	*Phosphate (mmol/l)*	*Alkaline phosphatase activity (U/l)*	
1	1·54	3·0	640	<156
2	1·25	4·4	481	50
3	1·03	2·7	1387	<40
4	1·91	1·7	310	>1000
5	1·65	2·8	156	>100
6	1·4	2·8	251	52
7	1·6	2·9	Not measured	Not measured
8	1·53	Not measured	276	23
Reference ranges	2·2–2·67	0·83–1·78	100–1000	120–410 (with normal serum calcium concentration)

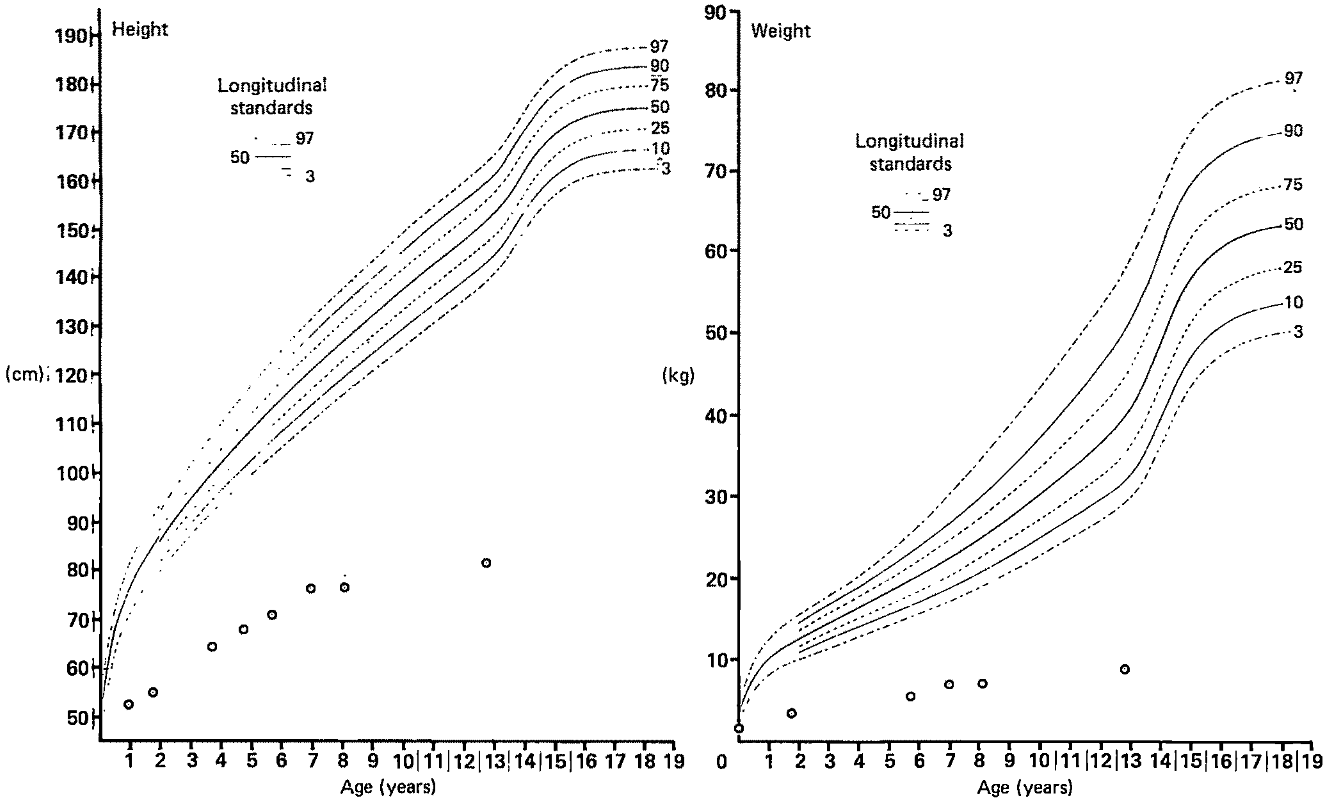


Figure 3 Growth charts of index case.

and head circumference of 45·0 cm (table 2). He had clinical evidence of heart failure and an enlarged liver, both of which were thought to be secondary to iron overload from repeated transfusion, as the serum ferritin concentration was grossly raised at 11804 μg/l (reference range 40–300). Although the corrected serum calcium concentration has been maintained within the reference range on up to 80 μg of 1α-hydroxycholecalciferol/day the renal ultrasound scan shows extensive generalised nephrocalcinosis.

CASES 2–8

Pedigrees (fig 1)

All eight children were the product of seven consanguinous marriages between first cousins of Middle Eastern origin. There was no evidence that any of the families were inter-related. Four of the children were boys, and four girls. Cases 1 and 2 were brothers, and in four of the remaining six families there had been a further five similarly affected siblings with dysmorphism, hypocalcaemia, and recurrent infections who died in infancy.

Auxological data (table 2)

The standards of Tanner *et al* have been used for all the auxological data.[1–3]

The birth weights of the seven patients for whom data are available are all below the 10th centile when adjusted for gestational age, indicating that the onset of the failure to thrive was prenatal. Measurements of height, weight, and head circumference made at the time of the latest assessment have been given, and show that all the variables are <-2 SD scores (approximates to third centile) for age and sex. There are no discrepancies among the height, weight, and head circumference SD scores.

Developmental delay

All the patients were severely developmentally retarded. Motor milestones were especially affected, with only case 1 being able to walk, and none of the other seven children being able to crawl or stand unsupported. Speech was limited to babble in all children except case 1. Although cardiorespiratory arrest secondary to hypocalcaemia had occurred in two of the children (cases 2 and 3), this could not account for the severe developmental delay in the other six.

Hearing was normal, although case 4 had bilateral perforated tympanic membranes that were colonised with *Pseudomonas aeruginosa*. Vision was also considered to be normal in all patients, although case 3 had cataracts, presumably secondary to hypocalcaemia.

INVESTIGATIONS

Hypocalcaemia (see table 3)

All eight patients presented with hypocalcaemia in the neonatal period, as did five affected siblings who died in infancy. Radioimmunoassay of the amino terminal human parathyroid hormone concentrations was carried out in seven of the children, and was inappropriately low for the serum calcium in six, confirming hypoparathyroidism. In the seventh child (case 4) the parathyroid hormone concentration was grossly raised (>1000 ng/l) on three occasions both with and without treatment, suggesting a biologically inert parathyroid hormone. Treatment with 1α-hydroxycholecalciferol in a total daily dose of 0·3—1·2 μg/day and calcium supplementation of 8·1–10·8 mmol/day have returned calcium concentrations to normal in all patients.

Skeletal survey

Skeletal surveys of all the patients were reviewed. Medullary stenosis of long bones was noted in seven patients and is most clearly seen in the forearm bones and the metacarpals. Other skeletal abnormalities included a valgus deformity of the femoral neck (n=2) and terminal acro-osteolysis in the distal phalanges (n=1).

Immune function

Three of the children (cases 2, 3, and 5) presented in the neonatal period with septicaemia and there was evidence that at least three further affected siblings had died in infancy of overwhelming infection.

Immunoglobulin concentrations were normal in three children in whom they were measured, but four children (cases 3, 4, 5, and 8) had reduced numbers of all T lymphocyte subsets. Case 3 was given thymic factor twice weekly in a dose of 1 mg/kg for two years until immune function had return to normal. Case 4 had abnormal polymorph mobility, in addition, but this was thought to be secondary to nutritional factors.

Other investigations

Glucagon stimulation tests of growth hormone release (100 μg/kg given intramuscularly) were carried out on three of the patients, with peak serum growth hormone concentrations of 6·1, 7·8, and 8·7 μg/l (12·2, 15·6, and 17·4 mU/l), respectively. Thyroid function was normal in all patients.

Liver function tests were carried out in five children; two have always had normal levels and three had increased transaminase activities. Case 1 has had grossly abnormal liver function tests (reference ranges given in parentheses)—bilirubin concentration 35 μmol/l (<17), alanine aminotransferase activity 156 U/l (6–16), aspartate aminotransferase activity 309 U/l (6–16), and γ glutamyltransferase activity 855 U/l (10–50)—which were thought to be secondary to iron overload as a result of repeated blood transfusion for thalassaemia major. Case 3 has had a liver biopsy specimen taken, which showed reactive hepatitis but no evidence of chronic liver disease. The abnormal liver function tests in this patient (bilirubin 144 μmol/l, alanine aminotransferase 144 U/l, γ glutamyltransferase 900 U/l) improved spontaneously with no treatment. Case 5 has had persistent unexplained increase in transaminase activities (alanine aminotransferase 283 U/l and aspartate aminotransferase 133 U/l).

Six of the patients have had chromosome analyses performed, including Giemsa banding, and no abnormality has been found.

Discussion

The association of extreme failure to thrive, dysmorphic features, developmental delay, abnormal skeletal survey, and hypoparathyroidism has not to our knowledge been previously reported. The similarity of the pattern of anomalies in the eight children described and in five further affected siblings indicates a syndrome that has a common mode of determination. Though this new syndrome does have some features in common with the Kenny-Caffey syndrome, such as short stature and hypocalcaemia (caused by hypoparathyroidism or an abnormal parathyroid hormone) in association with abnormalities in the skeletal survey, it differs substantially in that our group of patients had no evidence of macrocephaly, and were all developmentally delayed.[4–7] DiGeorge's syndrome, a defect of the third and fourth branchial arches, may present with hypoparathyroidism and immune dysfunction, although both are commonly transient.[8] Most patients with DiGeorge's syndrome, however, present with congenital heart disease, and though echocardiography was not carried out on our patients none had any abnormal findings on clinical examination.[9]

As the consanguinuity rate approaches 60% in some populations within the Middle East, the emergence of an autosomal recessive condition is more likely and this is the presumed mode of inheritance of this syndrome.[10–12] Larger numbers of patients will have to be identified before its genetics can be more fully elucidated; in the meantime recognition of affected children will allow earlier prescription of appropriate treatment.

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Hyperinsulinaemic hypoglycaemia in small for dates babies

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Abstract

Blood glucose concentrations were measured prospectively in 27 small for dates infants in the first 48 hours after birth: 10 infants became hypoglycaemic. Of these, five had inappropriately raised plasma insulin concentrations. Plasma free fatty acids were lower and carbohydrate intake higher in these five infants, further supporting the diagnosis of hyperinsulinism. The hypoglycaemia recurred in four of the five hyperinsulinaemic infants, but in none of those who were not hyperinsulinaemic.

Hyperinsulinism is common in small for dates babies. It is important to recognise this because hypoglycaemia is likely to recur and appropriate treatment is needed to prevent long term sequelae.

Neonatal hypoglycaemia is a common problem, the causes of which are often attributed to glycogen depletion and immature gluconeogenesis. Hyperinsulinism is another cause that is well recognised in infants of diabetic mothers, and in those with the Beckwith-Wiedemann syndrome, erythroblastosis fetalis, and nesidioblastosis, but nevertheless is still widely regarded as being relatively uncommon.[1] We have previously reported six infants who presented over a short period to the Hospital for Sick Children, London, however, who had unequivocal hyperinsulinism and who did not fit into any of these categories. Three of the infants were small for dates and three had been asphyxiated at birth.[2] As these patients could have been highly selected we have studied prospectively small for dates infants born in one year in one unit to determine the frequency of hypoglycaemia with current management and to see if hyperinsulinism was frequent.

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Patients and methods

PATIENTS

Any infant weighing less than the 10th centile for gestational age born at Princess Anne Hospital and admitted to the special baby care unit during a period of one year was eligible for study, provided full parental consent was given. Infants of mothers with carbohydrate intolerance were excluded. The total volume of blood required for the investigations was a maximum of 9 ml, and we therefore planned also to exclude infants with a birth weight of less than 1500 g.

All the babies had blood glucose concentrations monitored by capillary puncture as part of the routine in the unit. The blood samples for this study were taken at the same time from peripheral veins.

All studies were approved by the ethical committee of Southampton and South West Hampshire Health Authority and were explained in full to the parents.

METHODS

Blood was collected in the first six hours after birth for blood glucose, free fatty acids, insulin, and C peptide concentrations. Further samples for the same measurements were taken as near to 12, 24, and 48 hours as possible.

Blood for measurement of glucose was collected into ice cold 0·4M perchloric acid in tared bottles, spun, and refrigerated within 15 minutes of collection. Separation and analysis was completed within two to three days. The sample for free fatty acids, insulin, and C peptide measurement was collected into a cold lithium heparin bottle, spun, separated, divided into two, and immediately frozen in plain tubes.

Samples for blood glucose concentration was analysed using standard enzymatic methods on an Abbott ABA 100 automatic spectrophotometer.[3 4] Assay of insulin and C peptide concentrations were by standard radioimmunoassay methods and the detection limits were 25 pmol/l for insulin and 75 pmol/l for C peptide. Where possible urine was collected from the infants at the same or close to the time the blood samples were taken and immediately frozen in a plain tube for C peptide and creatinine measurements.

Hypoglycaemia was defined as a blood glucose concentration of less than 2·2 mmol/l and hyperinsulinism as plasma insulin concentration of more than 30 pmol/l (4 mU/l) during hypoglycaemia.

Results

Twenty nine small for dates infants were entered into the study but two had only one blood sample collected and have been omitted. No infant was less than 32 weeks' gestation by dates, scan, or by postnatal assessment, and most were over 35 weeks (table 1). Inadvertently three patients were included who were weighed less than 1500 g (1440, 1450, and 1090 g). The smallest baby was hypoglycaemic and all have been included in the analysis.

Seventeen of the 27 infants remained normoglycaemic throughout the study (table 1) and 10 of the 27 infants became hypoglycaemic, although none was symptomatic (table 1).

Table 1 Details of babies in the study

	Normoglycaemic group	*Hypoglycaemic group*
Blood glucose concentrations	Normoglycaemic throughout (blood glucose >2·2 mmol/l)	One or more blood glucose <2·2 mmol/l
No of babies	17	10
Delivery:		
Normal	5	5
Forceps	4	0
Caesarean section	8	5
Gestation (weeks)	34–40	32–40
Mean (range) birth weight (g)	1960 (1440–2330)	1930 (1090–2480)
No (%) mothers having intravenous treatment*	12 (70)	7 (70)
Apgar score:		
<5 at 1 minute	3	1
<5 at 5 minutes	0	0

*4–5% glucose.

MATERNAL MEDICATION

None of the mothers had been or was on any medication during pregnancy. Nineteen had an intravenous infusion of 4–5% glucose during labour. Seven of the 19 infants born to these mothers subsequently became hypoglycaemic (table 1).

INFANT FEEDS

As a routine all infants were given either an oral or nasogastric feed within three hours of birth. Healthy infants were given milk feeds alone, 60 ml/kg/day on the first day and then 85 ml/kg/day on day two.

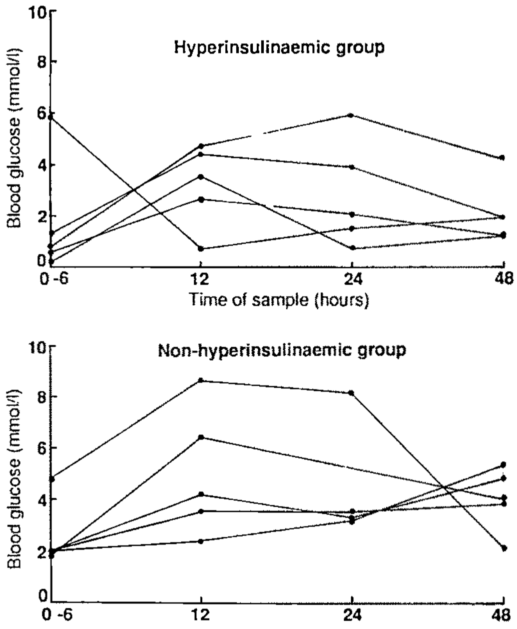
INTRAVENOUS TREATMENT

In addition to their routine feeds 12 babies were given intravenous fluids during this time. Six of them were hypoglycaemic. The other six were not hypoglycaemic but their clinical condition gave rise to other concerns. Two of the 12 infants were also given a bolus dose of glucose in addition to the infusion because of a low reading on BM–Test reagent strips (Boehringer), although only in one infant was hypoglycaemia confirmed when the blood glucose concentration was measured in the laboratory.

HYPOGLYCAEMIC BABIES

Five of the 10 hypoglycaemic babies had appropriate insulin concentrations throughout the time they were studied (table 2). The other five had one or more inappropriately raised insulin concentration during hypoglycaemia. Blood glucose concentrations were generally lower in the hyperinsulinaemic babies (figure) and all had blood glucose concentrations of less than 1·3 mmol/l within the first 12 hours after birth. In four of the five hyperinsulinaemic babies the hypoglycaemia recurred (figure) but it did not do so in any of the non-hyperinsulinaemic group. Although the data were incomplete the plasma free fatty acid concentrations at the time of hyperinsulinaemic hypoglycaemia were lower (mean 0·45 mmol/l, n=4) compared with the other infants whose insulin concentrations were appropriate for their blood glucose concentrations (mean 0·52 mmol/l, n=3). The hyperinsulinaemic infants all received milk orally and glucose intravenously. Two of these infants required glucose infusion rates of more than 10 mg/kg/min. Only two of the non-hyperinsulinaemic infants had intravenous treatment, both at normal glucose infusion rates (<8 mg/kg/min) at times when they were not being fed.

Plasma C peptide concentrations were higher in the hyperinsulinaemic babies (mean 459 pmol/l) than in the other hypoglycaemic babies (mean 265 pmol/l). The mean concentration in



Blood glucose concentrations during the first 48 hours of life.

Table 2 Blood glucose, insulin, and C peptide concentrations during hypoglycaemia

Infant No	*Age (hours)*	*Glucose (mmol/l)*	*Insulin* (pmol/l)*	*C peptide* (pmol/l)*
		Non-hyperinsulinaemic group		
1	<6	2·0	<25	248
2	<6	2·0	<25	<75
3	<6	2·0	<25	248
4	48	2·1	<25	682
5	<6	1·8	<25	87
		Hyperinsulinaemic group		
6	<6	0·6	46	155
7	<6	0·2	179	310
7	48	1·2	79	465
8	<6	0·7	49	403
9	48	1·9	82	682
10	12	0·7	66	744

*Detection limit for insulin is 25 pmol/l and for C peptide 75 pmol/l.

the latter group was similar to the C peptide concentrations in those babies who remained normoglycaemic (mean 319 pmol/l). Overall, however, there was a poor correlation between the plasma insulin and C peptide concentrations (for example, babies 4 and 7, table 2).

It was not possible to collect simultaneous blood and urine samples from all the patients. Twelve samples were collected from nine infants. Urinary C peptide concentrations ranged between 372 and 3100 pmol/l (242 and 1803 pmol/mmol creatinine). No correlation was found between plasma and urinary C peptide concentrations. The infant with the highest urinary C peptide concentration had one of the lowest plasma values.

Discussion

Many factors probably contribute to hypoglycaemia in small for dates infants. These could include lack of exogenous substrate supply, depletion of hepatic glycogen stores, defective gluconeogenesis, hyperinsulinism, and adrenocortical insufficiency.[1] Some of the factors were examined by Le Dune who studied the response of small for dates babies to an intravenous glucose load or intramuscular glucagon in the first six hours of life before the first feed.[5 6] She concluded that both hyperinsulinism and glycogen depletion contributed to the hypoglycaemia. Before the first feed insulin is still likely to be the dominant hormone, however, and giving a bolus of glucose intravenously may stimulate excess insulin release. The purpose of this study was to see if hyperinsulinism was responsible for hypoglycaemia in small for dates babies with current management. The only criteria for entry to the present study was a birth weight less than the 10th centile for gestational age, although we intended to exclude babies weighing less than 1500 g because of the volume of blood necessary. One very small for dates infant (1090 g at 32 weeks) was inadvertently included because of his hypoglycaemia and has been left in the analysis as this does not affect the conclusions. No infant was less than 32 weeks' gestation and most were near term. Although not all eligible infants were studied because of failure to obtain the blood samples, those lost were thought to be lost randomly.

Of the 27 infants studied 10 became hypoglycaemic and half of these showed evidence of hyperinsulinaemia. These babies also had higher carbohydrate requirements and slightly lower free fatty acid concentrations supporting the diagnosis of hyperinsulinism.[1] The hyperinsulinaemic babies also tended to have lower blood glucose concentrations than the non-hyperinsulinaemic. The mechanism responsible for the hypoglycaemia in the other five babies is not clear. Some may have been relatively and temporarily glucagon deficient.[7]

We can only speculate why hyperinsulinism occurs in small for dates infants. The most likely suggestion is that it is a persistent fetal state in which islet organisation has not yet been completed and insulin is still the dominant hormone.[1 8]

Insulin and C peptide are produced in equimolar quantities but they are removed from the circulation at different rates. Insulin is cleared by the liver, with a half life of four to five minutes, whereas C peptide is cleared by the kidney, with a half life of 11 to 30 minutes.[9] It has been suggested that peripheral plasma C peptide measurements might be more helpful than peripheral plasma insulin in assessing beta cell function,[10] because of C peptide having a longer half life, the assay being relatively more sensitive, and unaffected by variations in hepatic fractional extraction in response to food. However, we found a poor association between plasma insulin and C peptide concentrations in peripheral blood. We suggest that assay of C peptide is not a good means of assessing beta cell function in neonates, possibly because of renal immaturity and hence reduced renal clearance.

Although hyperinsulinism was clearly demonstrated in 1972,[5 6] in small for dates babies it is still not adequately recognised. This study confirms that hyperinsulinism is still frequently a cause of hypoglycaemia in small for dates infants. These infants have increased glucose requirements and go on having problems with hypoglycaemia longer than those hypoglycaemic babies who are not hyperinsulinaemic. We suggest that babies with blood glucose concentrations of less than 1·3 mmol/l are more likely to have hyperinsulinaemia. It has recently been emphasised that we are not treating neonatal hypoglycaemia aggressively enough in view of the neurodevelopmental sequelae.[11 12] This is particularly important when the cause is hyperinsulinism because of the inhibition of lipolysis and hence the lack of alternative fuels for energy metabolism. Hyperinsulinaemia should be recognised in small for dates babies so that more intensive treatment can be started and continued.

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Treatment of chronic liver disease caused by 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase deficiency with chenodeoxycholic acid

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Abstract

Deficiency of 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase, the second enzyme in the sequence that catalyses the synthesis of bile acids from cholesterol, leads to chronic liver disease in childhood as well as to malabsorption of fat and fat soluble vitamins. A 4 year old boy with this condition has been successfully treated by oral administration of a bile acid—chenodeoxycholic acid. He had been jaundiced since birth, grew poorly because of rickets, and had severe pruritus. Plasma transaminase activities were persistently raised. Chenodeoxycholic acid 125 mg twice daily for two months, and then 125 mg daily, cured his jaundice and pruritus, returned his transaminase activities to normal, and eliminated the need for calcitriol for prevention of rickets. On this treatment he has so far remained well for two years. A diagnosis of 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase deficiency should be considered in any child with unexplained chronic hepatitis or cirrhosis, especially if the liver disease is accompanied by a clinically obvious malabsorption of fat soluble vitamins. A simple colorimetric test of the urine confirms the diagnosis and effective treatment can be started.

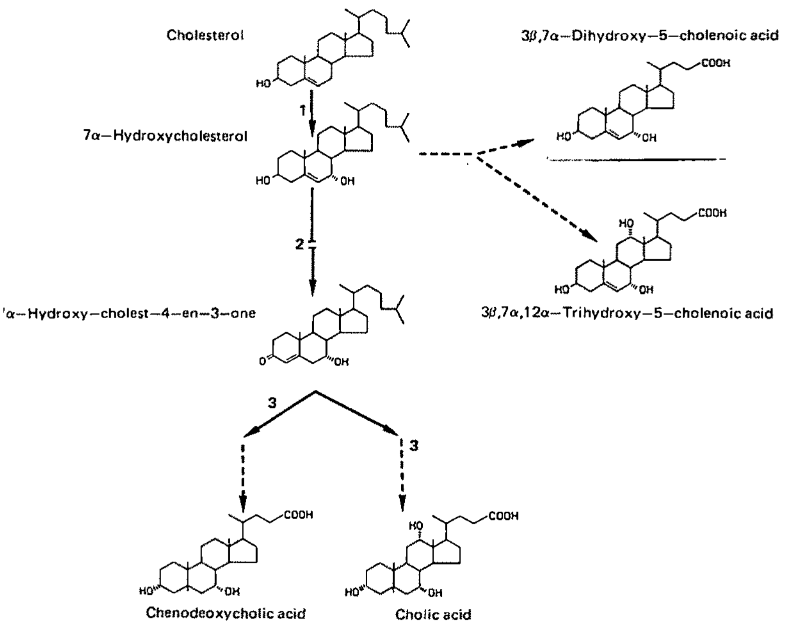

Figure 1 Pathway for the synthesis of bile acids from cholesterol. Reaction 1 catalysed by cholesterol 7α-hydroxylase is inhibited by chenodeoxycholic acid (feedback inhibition). Reaction 2 is catalysed by 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase; deficiency of the enzyme leads to synthesis of 3β-hydroxy-Δ5 bile acids. Reaction 3 is catalysed by 3-oxo-Δ4-steroid 5β-reductase.

In the principal pathway for the synthesis of chenodeoxycholic acid and cholic acid from cholesterol in the liver (fig 1), the first (and rate limiting) step is catalysed by cholesterol 7α-hydroxylase.[1] 7α-Hydroxycholesterol is then converted to 7α-hydroxy-cholest-4-en-3-one by a 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase/isomerase. This enzyme was shown to be deficient in the cultured fibroblasts of a boy from Saudi Arabia who was one of three siblings who had chronic cholestatic liver disease.[2 3] When first studied at the age of 3 months, the patient had undetectable concentrations of chenodeoxycholic acid and cholic acid in his plasma despite clear evidence of cholestasis. Instead of synthesising the usual primary bile acids, he was producing large amounts of 3β, 7α-dihydroxy-5-cholenoic acid and 3β, 7α, 12α-trihydroxy-5-cholenoic acid—that is, bile acids formed from precursors in which normal conversion of the 3β-hydroxy-Δ5 structure to a 3α-hydroxy-5β (H) structure had not occurred. The unsaturated bile acids were present at high concentration in the urine in sulphated form. They did not seem to be able to promote bile acid dependent bile flow and the absorption of fat and fat soluble vitamins from the intestine. The infant had conjugated hyperbilirubinaemia from birth, steatorrhoea, and low plasma concentrations of vitamins A, D, and E. There was also evidence that either the production of abnormal bile acids or the failure to produce cholic and chenodeoxycholic acids was causing progressive liver damage. The patient had raised transaminase activities and liver biopsy specimens taken from his affected siblings showed a giant cell hepatitis that progressed to a micronodular cirrhosis.

We argued that if this patient were given chenodeoxycholic acid or cholic acid, or both, these bile acids would be retained within the enterohepatic circulation and could promote bile acid dependent bile flow and facilitate micellar solubilisation of fats and fat soluble vitamins. As cholesterol 7α-hydroxylase is inhibited by cholic and chenodeoxycholic acids, we could also hope for a reduction in the synthesis of abnormal metabolites of 7α-hydroxycholesterol. This report describes the progress of this patient who was not treated until the age of 4·3 years, at which time he was started on treatment with chenodeoxycholic acid.

Case report

The family history and the initial presentation of this patient have previously been described.[2]

He was lost to follow up but then presented at the King Faisal Specialist Hospital and Research Centre, Riyadh at the age of 2·8 years. A variable degree of jaundice had persisted since infancy with dark urine and stools that were pale or yellow. He had severe pruritus, had retarded growth, and did not walk until the age of 2 years. His parents had noted bowing of his legs. On examination his weight was 13·6 kg (25th centile), height 82·5 cm (below the 3rd centile), and head circumference 50·5 cm (50th centile). Growth failure was associated with clinical rickets, with widening of wrists and a rachitic rosary in addition to his bowed legs. His liver was palpable 4 cm from the right costal margin and was firm. The spleen was not palpable.

Investigation confirmed persistent jaundice, hepatic dysfunction and vitamin D malabsorption. The plasma bilirubin concentration was 41 μmol/l (direct 36 μmol/l); alanine aminotransferase activity 56 IU/l (reference range 10–25); aspartate aminotransferase activity 57 IU/l (reference range 10–40); and alkaline phosphatase activity 1085 IU/l (reference range 100–300). The albumin concentration was 47 g/l and prothrombin time and partial thromboplastin time normal. Calcium concentration was 1·67 mmol/l (reference range 2·13–2·62) and phosphate concentration 1·36 mmol/l (reference range 1·29–1·78). Radiography of the wrist showed florid rickets. Ultrasound scan of the liver confirmed that it was enlarged, with normal echogenicity.

Between the ages of 2·8 and 4·3 years he was treated with supplements of fat soluble vitamins. The vitamin D was given as the 1,25-dihydroxy derivative (calcitriol, 0·5 μg/day). His rickets improved clinically, radiologically, and biochemically (calcium concentration 2·44 mmol/l, alkaline phosphatase activity 300 IU/l). The jaundice and raised transaminase activities persisted, however (fig 2). Chenodeoxycholic acid was undetectable in plasma (as it had been at 3 months) but some cholic acid was present in both plasma (<4·3 μmol/l) and in bile.

At the age of 4·3 years, treatment with chenodeoxycholic acid (Chendol, Weddel) was started, initially in a dose of 125 mg (one capsule) twice daily (18 mg/kg/day), reducing to 125 mg daily after two months. At the time of writing treatment has continued for two years. After the first two months he was already feeling better. He was more active and his appetite had improved. The pruritus had disappeared and his urine had become normal in colour. The size of the liver was unchanged. His plasma bilirubin concentration had fallen to within the reference range for the first time in his life and the transaminase activities were almost normal (alanine aminotransferase 35 and aspartate aminotransferase 44 IU/l). The improvement was maintained over the ensuing months (fig 2) and he had no problem with diarrhoea as a result of the chenodeoxycholic acid treatment.

By the age of 5·3 years, he had achieved considerable catch up growth. His weight was 19·2 kg (50th centile) and height 105 cm (above 10th centile) but limb deformities as a result of his previous rickets were still evident and he had carious teeth. The liver was palpable 5 cm from the costal margin (span 8·5 cm). Bilirubin concentration and transaminase activities were all within the reference ranges. His serum cholesterol concentration was normal (4·86 mmol/l). Plasma chenodeoxycholic acid concentration was 1·6 μmol/l, which is within the physiological reference range. Skeletal radiographs confirmed complete healing of the rickets. Plasma 25-hydroxyvitamin D and vitamin E concentrations were at the upper limit of the reference range when his dietary intake was supplemented with 800 units of vitamin D and 200 mg of α-tocopherol acetate daily. The vitamin D supplement was subsequently reduced to 240 units daily and the alkaline phosphatase activity has remained normal.

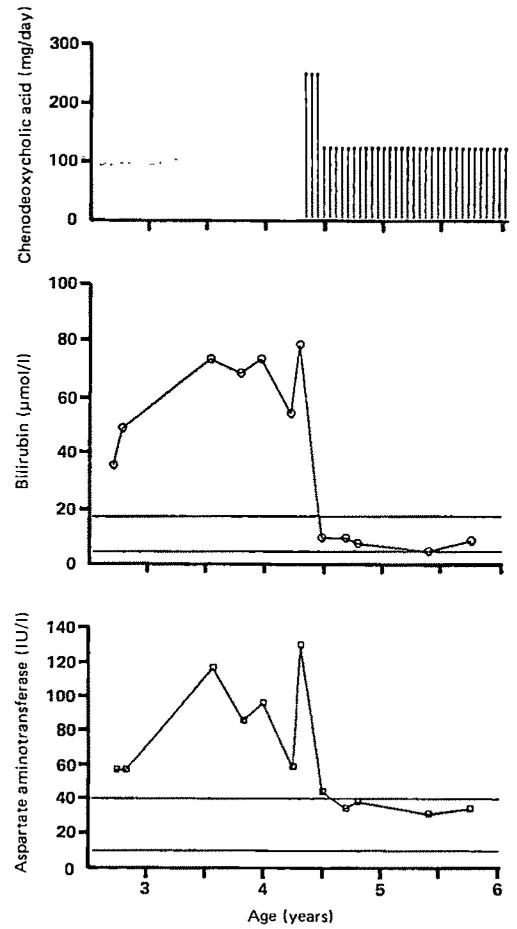

Figure 2 Effect of treatment with chenodeoxycholic acid started at the age 4·3 years on the patient's bilirubin concentration and aspartate aminotransferase activity.

Discussion

Without permission to do a liver biopsy it was difficult to estimate the extent of our patient's liver disease at the age of 4 years. It seemed unlikely that it was as severe as that of his brother, who had an established micronodular cirrhosis by the age of 3·8 years.[2] The index case had no signs of portal hypertension and plasma albumin concentration and clotting times were normal. The bilirubin concentration and transaminase activities, though persistently raised, were slightly lower than they had been at the age of 3 months. It would seem therefore that liver disease in siblings with 3β-hydroxy-Δ5-

C_{27}-steroid dehydrogenase deficiency may progress at different rates. This may be related to the degree of synthesis of normal bile acids that occurs in the different siblings. In the absence of the normal 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase enzyme, oxidation of 7α-hydroxycholesterol or 3β-hydroxy-Δ5 bile acids might be catalysed by hepatic 3β-hydroxy-Δ5-steroid dehydrogenases not normally concerned in bile acid synthesis,[4] or by similar enzymes in the gut flora.[5] In the case of our patient, some glycocholic acid was found in bile—as much as 30% of the total C_{24} bile acids at the age of 4·3 years.

Our index case had severe pruritus. The concentration of cholic acid in his plasma was <4·3 μmol/l (which is within the reference range) and chenodeoxycholic acid was undetectable. We must conclude, therefore, that pruritus can be caused either by bile acids with a 3β-hydroxy-Δ5 structure, or by the accumulation of something other than bile acids in patients with cholestasis.

Our patient continued to have severe malabsorption of vitamin D until treatment with bile acids was started. Treatment of his rickets required the use of calcitriol which, unlike dietary vitamin D, can be absorbed directly into the portal circulation.[6]

The rationale for treatment with bile acids has been given in the introduction to this paper. To create a roughly normal pool of bile salts it would have been necessary to give both cholic and chenodeoxycholic acid; cholic acid is not readily available for therapeutic use. On the other hand, chenodeoxycholic acid and ursodeoxycholic acid are extensively used to treat gall stones. Chenodeoxycholic acid is also effective in the treatment of another inborn error of bile acid synthesis, cerebrotendinous xanthomatosis, in which the aim of treatment is to give enough bile acid to inhibit cholesterol 7α-hydroxylase and hence reduce the synthesis of bile alcohols from cholesterol.[7 8] Ursodeoxycholic acid does not inhibit cholesterol 7α-hydroxylase,[9] or suppress the production of abnormal metabolites in cerebrotendinous xanthomatosis.[10] We wanted to suppress the synthesis of abnormal metabolites and so chenodeoxycholic acid seemed the best choice. Chenodeoxycholic acid has, however, some hepatotoxic properties when used in patients with gall stones,[11 12] and it is also considered to contribute to the damage to hepatocytes that occurs in patients with cholestasis.[13] Thus before starting treatment with chenodeoxycholic acid we confirmed that concentrations of chenodeoxycholic acid were low in both bile and in blood, and during treatment we ensured that plasma concentrations did not rise above the physiological range.

The choice of dose of chenodeoxycholic acid that we used was somewhat empirical and based partly on the fact that 125 mg capsules are readily available. We estimated that a 4 year old boy with a normal pool of bile acids should synthesise and lose in the faeces about 3 mg/kg/day of bile acids and so this was the minimum dose.[14] The dose of chenodeoxycholic acid used in adults for dissolution of gall stones and for suppression of abnormal metabolite synthesis in cerebrotendinous xanthomatosis is about 12·5 mg/kg/day.[7] Patients with cerebrotendinous xanthomatosis have some endogenous chenodeoxycholic acid synthesis and we felt that a higher dose may be required for our patient. Thus a dose of two capsules (18 mg/kg/day) was chosen, reducing to one capsule when there was no longer any biochemical evidence of cholestasis.

Clinically the benefit of chenodeoxycholic acid was evident within two weeks. The bilirubin concentration was normal within four weeks, and the aspartate transaminase activity by three months. This meant that we had a baseline of normal liver function tests against which to look for possible long term toxicity of chenodeoxycholic acid but none has been detected during almost two years.

In addition to the possible toxic effects of chenodeoxycholic acid, we had two other concerns about the treatment. The first was that if high doses of vitamin D were given, and absorption of fat soluble vitamins was stimulated by producing effective intestinal bile salt concentrations, our patient might develop the effects of hypervitaminosis D. Thus the calcitriol was discontinued before starting chenodeoxycholic acid, and a modest vitamin D supplement (800 units) was given. On this regimen no hypercalcaemia was detected and plasma 25-hydroxyvitamin D remained within the reference range. To avoid hypervitaminosis A, high doses of vitamin A were also avoided during treatment with chenodeoxycholic acid.

A second cause of concern was the possibility of raised serum concentrations of cholesterol during treatment with bile acids.[15] Catabolism to bile acids is an important way of eliminating cholesterol. Treatment with chenodeoxycholic acid should reduce cholesterol catabolism by inhibiting cholesterol 7α-hydroxylase. The treatment should also improve absorption of cholesterol from the gut and these two mechanisms might together contribute to a rise in serum cholesterol concentration. While receiving treatment our patient's serum cholesterol concentration was within the reference range.

The success of treatment with chenodeoxycholic acid in 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase deficiency makes it important that this diagnosis be considered in any child with chronic hepatitis particularly if it is accompanied by fat soluble vitamin malabsorption. The diagnosis can be made in any clinical chemistry laboratory by a colorimetric test on the urine (the Lifschütz reaction) and it can then be confirmed by fast atom bombardment mass spectrometry or gas chromatography/mass spectrometry in specialised centres.[2] If the latter methods are used to screen for inborn errors of bile acid metabolism, patients with reduced activity of 3-oxo-Δ4-steroid 5β-reductase (the third enzyme in the sequence leading from cholesterol to chenodeoxycholic acid) will also be detected because the urine contains characteristic 3-oxo-Δ4 bile acids.[16 17] We would not advocate the use of chenodeoxycholic acid in these patients without careful assessment for a number of reasons.

Firstly, the patient may not have a primary defect of 3-oxo-Δ4-steroid 5β-reductase but some other disease such as fumaryl acetoacetase deficiency.[16]

Secondly, plasma concentrations of chenodeoxycholic acid in these patients are usually considerably increased. It is likely that concentrations in hepatocytes are also increased and this may be damaging.[13]

Thirdly, experience has shown that chenodeoxycholic acid can be harmful. Giving chenodeoxycholic acid to one infant excreting 3-oxo-Δ4 bile acids in his urine aggravated his cholestasis and transaminase activity increased (H Nazer, T Gunasekaran, J Sjövall, unpublished observations). Bilirubin concentration and transaminase activities then returned to pretreatment measurements when chenodeoxycholic acid was withdrawn.

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X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis

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Abstract

The clinical data of 18 patients with X linked hypophosphataemia were analysed retrospectively. The height data were expressed as SD scores. There was no difference in the final height of patients treated with vitamin D (or 1,25-dihydroxyvitamin D) and phosphate for at least two years (n=12) and that of 16 hypophosphataemic family members who had never been treated. The mean final SD score (−2·07) of treated patients, however, was significantly higher than the value before treatment (−2·79), which indicated an average absolute height gain of 4–4·5 cm compared with the expected height values. Six of the treated patients developed ultrasonographically detectable nephrocalcinosis with normal renal function. The daily phosphate intake and excretion of patients with nephrocalcinosis was significantly higher than that of patients with normal renal morphology. There was no difference in the doses of vitamin D between the two groups. The average urinary calcium:creatinine ratio of the two groups was similar to and below the hypercalciuric 0·6 mmol:mmol limit. The group with nephrocalcinosis, however, had a higher incidence of hypercalciuric episodes than the group without nephrocalcinosis (12 in 130 observations compared with six in 334 observations, respectively). The benefits and risks of treatment of patients with X linked hypophosphataemia must be further evaluated. The high dose of phosphate seems to be an important factor in the development of nephrocalcinosis in this group of patients.

Familial hypophosphataemia is a type of hereditary, vitamin D resistant, rickets that is characterised by sustained hypophosphataemia, relative hyperphosphaturia, normocalcaemia, rachitic bone changes, and growth retardation.[1-5] The inheritance is X linked dominant.[3 4] Hypophosphataemia is the result of impaired renal reabsorption and intestinal absorption of phosphate and according to recent data inappropriate low serum concentrations of 1,25-dihydroxyvitamin D (1,25-DHVD) either in absolute terms or compared with the serum phosphate concentration.[5-12] The conventional treatment of X linked hypophosphataemia consists of high doses of vitamin D and oral phosphate supplements. Vitamin D was replaced in recent studies by the active metabolite 1,25-DHVD.[6 7 13] In addition, thiazide diuretics have also been used to reduce urinary losses of phosphorus and calcium.[14]

The value of these treatments has, however, recently been questioned.[15] In addition, serious side effects such as osteomalacia[16] and nephrocalcinosis[17 18] have been reported. Transient hypercalciuria and hypercalcaemia are well known side effects of high doses of vitamin D and potent D vitamin analogues.[18] Calcium, however, is not the only constituent responsible for the growth of crystals in supersaturated urine. High doses of phosphate could also lead to the formation of relatively insoluble salts by at least two mechanisms: firstly, by the formation of calcium phosphate,[19 20] and secondly by provoking enteric hyperoxaluria by intestinal binding of calcium.[21]

The aim of the present study was to analyse the effects of the combined treatment with vitamin D and phosphate on the growth of patients with X linked hypophosphataemia, to find out the incidence of ultrasonographic renal calcification,[18] and to elucidate the role of the treatment in renal calcification.

Patients and methods

Between 1974 and 1989, 18 patients with X linked hypophosphataemia were treated with combined vitamin D (or 1,25-DHVD) and oral phosphate in our clinic.[22] Sixteen adult hypophosphataemic relatives who had not been treated during the growth period served as controls.

All treated patients were diagnosed by the presence of rachitic bone changes, the persistence of hypophosphataemia, relative hyperphosphaturia, normocalcaemia, high alkaline phosphatase activity, and normal serum concentrations of parathyroid hormone.[5 22] X linked dominant inheritance was confirmed by analysis of the pedigrees.

All patients visited our outpatient clinic at regular intervals: infants and young children every three weeks to two months and adolescents and young adults every three to six months depending on the intensity of treatment. Urinary excretion of calcium and phosphate, serum calcium and phosphate concentrations, and creatinine clearance were measured routinely. Calcium, phosphate, and creatinine were estimated by routine laboratory methods.

Hypercalcaemia was defined as a serum calcium concentration of over 2·75 mmol/l. Hypercalciuria was defined as urinary calcium:creatinine ratio above 0·6 mmol:mmol.[23]

All heights were expressed as standard deviations from the mean of the chronological age (SD scores).[15] All patients were recalled for ultrasonographic scanning of their kidneys. The examinations were performed and interpreted by one of us (PFH) without knowledge of the clinical state or details of the treatment.

Statistical analysis was by Student's *t* test for unpaired and paired data, and the χ^2 test.

Results

A total of 464 clinical observations of the 18 patients were considered. The mean age at the start of treatment was 5·8 years (range 5 months

Table 1 Treatment with phosphate, vitamin D, and 1,25-DHVD in patients with X linked hypophosphataemia at different ages

	Age group (years)							
	0–3 (n=6)		*3–14 (n=12)*		*14–18 (n=15)*		*>18 (n=11)*	
	No of patients	*Mean (SD) dose*	*No of patients*	*Mean (SD) dose*	*No of patients*	*Mean (SD) dose*	*No of patients*	*Mean (SD) dose*
Phosphate (mg/kg/day)	6	107 (48)	12	74 (30)	15	53 (30)	11	37 (19)
Vitamin D (units/kg/day)	3	1370 (798)	11	902 (405)	13	580 (365)	8	198 (108)
1,25-DHVD (ng/kg/day)	3	35 (6·4)	2	21 (5)	2	5 (0·6)	2	5 (0·3)

– 14·5 years), and at the time of the last visit 15·9 (range 3–24·5) years. The mean treatment time was 8·4 years (range 1–15), and the mean length of treatment during the growth period was 6·8 years (range 1–14).

Patients were usually treated with both oral phosphate supplements and vitamin D (or 1,25-DHVD). The daily doses relative to body weight of vitamin D, 1,25-DHVD, and phosphate were calculated for each patient for each visit to the clinic. Table 1 summarises the average doses calculated from these data for infants, children, adolescents, and adults.

In the age group 3–14 years one patient was changed from vitamin D to 1,25-DHVD, and his vitamin D and 1,25-DHVD doses are therefore both represented in the table. In the age group over 18 years, one patient received phosphate alone (table 1).

GROWTH DATA

The final height (expressed as SD score) of 16 patients with X linked hypophosphataemia who had received no treatment and 12 treated patients who reached their final height at the time of the study are compared in fig 1. There is no significant difference between the two groups (corresponding mean (SD) scores for patients who had received no treatment −2·27 (0·48), and for patients who had been treated −2·07 (0·47).

SD score before treatment and the last recorded score of the 12 patients who were treated for longer than two years and had already reached adulthood at the end of the study are shown in fig 2. The mean SD score increased from a pretreatment value of −2·79 to −2·07 ($p<0·02$, Student's *t* test for paired data). The same significant difference could be noted when the data of all 16 patients treated for longer than two years were compared ($p<0·02$).

CLINICAL DATA

Six of the 18 patients had abnormally increased echogenicity of the renal pyramids (nephrocalcinosis), and in four there was also acoustic shadowing (fig 3). All six patients received the most intensive treatment during the first two years of observation, which is therefore further analysed. Patients with nephrocalcinosis had significantly higher relative daily doses of phosphate than patients with normal renal ultrasonography (136·4 (30·4) mg/kg/day compared with 69·9 (22·1), $p<0·01$) (fig 4). There was no statistical difference between the doses of vitamin D and 1,25-DHVD in the two groups (fig 5).

There was no significant difference in the mean (SD) urinary calcium:creatinine ratio of patients with nephrocalcinosis and those with normal renal morphology (0·35 (0·19) and 0·22 (0·16) mmol:mmol, respectively). In contrast children with nephrocalcinosis had significantly higher phosphate:creatinine ratios (21·9 (11·9) and 9·1 (4·8) mmol:mmol, respectively; $p<0·01$).

The number of hypercalcaemic and hypercalciuric episodes is listed in table 2. One patient in each group had episode(s) of hypercalcaemia, which occurred three times in the patient with nephrocalcinosis. Hypercalciuria was observed at least once in all nephrocalcinotic patients but only in two of the 12 in the group who did not have

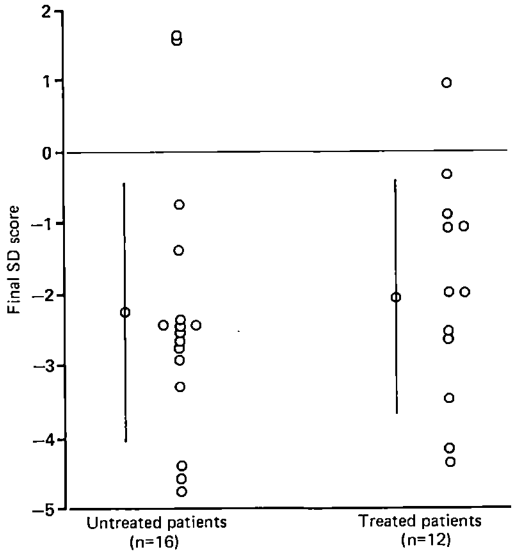


Figure 1 Growth of patients with hypophosphataemic rickets: adult height of 12 patients with X linked hypophosphataemia who were treated continuously and 16 patients who were never treated. The circle and vertical line indicate the mean (SD).

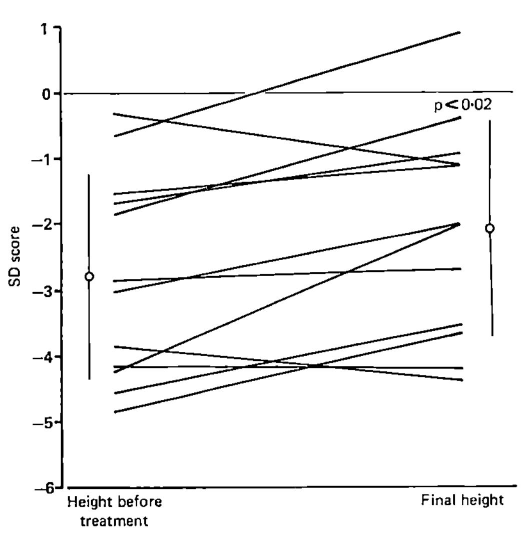
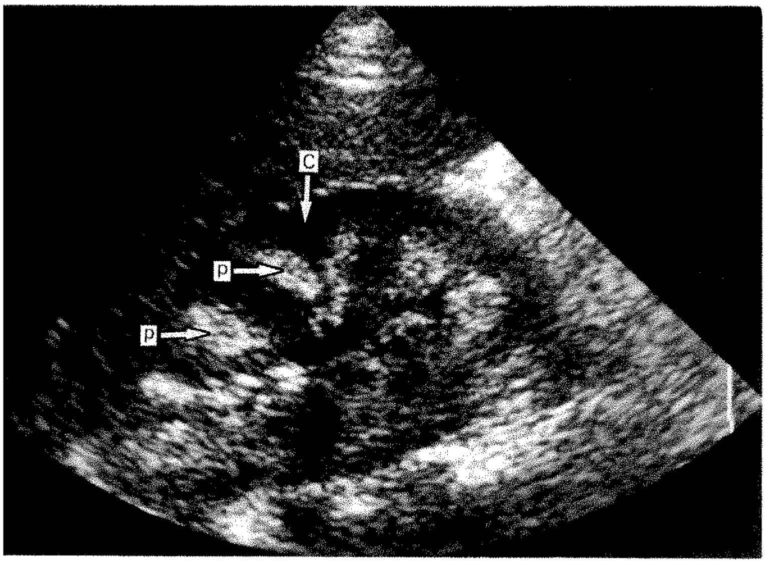


Figure 2 Growth of patients with hypophosphataemic rickets: height before treatment and final height of 12 adult patients with X linked hypophosphataemia who were treated for at least two years. The circle and vertical line indicate the mean (SD).



igure 3 Typical increased echogenicity of renal pyramids in a patient with X linked ypophosphataemia treated with 1,25-DHVD and phosphate. C=cortex; p=renal pyramids.

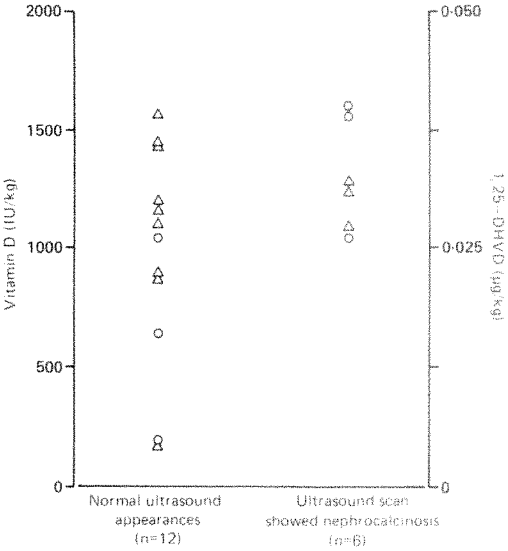


Figure 5 Daily doses of vitamin D (open triangles) and 1,25-DHVD (open circles) in children with X linked hypophosphataemia during the first two years of treatment.

nephrocalcinosis. Episodes of increased urinary calcium excretion were observed in 9% of the investigations in the nephrocalcinosis group, whereas in the group with normal renal sonography it was detected in only 2% of all periods considered ($\chi^2=13{\cdot}9$, $p<0{\cdot}01$).

There was no significant difference between the urine output (expressed as minute volume) of patients with X linked hypophosphataemia with increased calcium excretion and an age matched control group of 18 healthy children (mean (SD) 0·93 (0·21) compared with 0·83 (0·29) ml/min/1·73m,[2] respectively).

Considering all the data, we found no correlation between phosphate dose or urinary phosphate excretion and the change in the SD score in general, and in patients with nephrocalcinosis in particular.

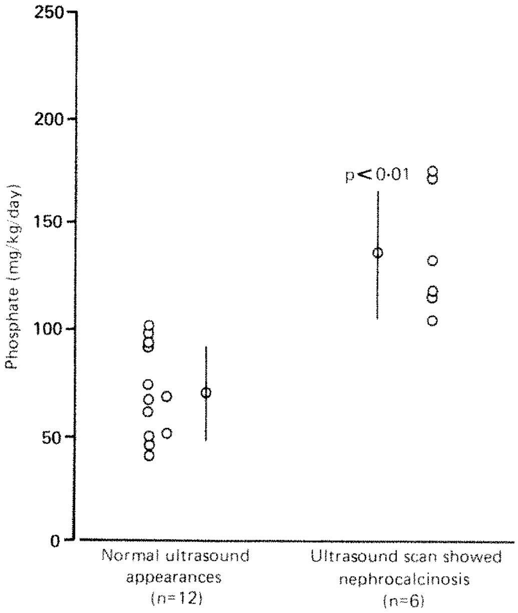


Figure 4 Daily doses of oral phosphate supplementation in patients with normal ultrasound appearances and those showing nephrocalcinosis. The circles and vertical line indicate the mean (SD).

Discussion

There are conflicting data about the benefits of combined vitamin D (or 1,25-DHVD) and phosphate treatment in children with X linked hypophosphataemia. Some authors have not found that the treatment had any positive effect on growth.[15 16] Other reports, based on growth velocity or a smaller number of children, claimed to prove significant improvement in treated patients.[9 10 23 24] The comparison of treated and untreated patients could be biased by the fact that untreated patients might have had a milder form of the disease than treated patients. Indeed in our series two hypophosphataemic family members were only detected by laboratory investigation, because they had normal SD scores and no bone deformities. On the other hand, all treated patients were referred to us because of growth retardation and overt signs of rickets. Thus the evaluation of the final height showed that there was no difference between the average SD scores of treated and untreated adults, but in the treated group there was a significant improvement in the SD scores suggesting that treatment had some positive effect on growth.

In the early stages of nephrocalcinosis radiography often fails to detect calcium deposition. Renal ultrasonography seems to be a more sensitive non-invasive method of diagnosis in such cases. The diagnosis is possible even before detectable functional disturbances occur.[17 18] In the present study six of the 18 patients with X linked hypophosphataemia had ultrasonographically proved nephrocalcinosis with no overt signs of functional renal damage. Our data confirm those of Goodyear *et al*[18]:11 of their 23 patients with X

Table 2 Hypercalcaemia, hypercalciuria, and ultrasonographic changes in patients with X linked hypophosphataemia

Ultrasonographic pattern	*No of patients/episodes of hypercalcaemia*	*No of patients/episodes of hypercalciuria*	*Total No of observations*
Normal (n=12)	1/1	2/6	334
Showed nephrocalcinosis (n=6)	1/3	6/12	130

linked hypophosphataemia investigated had ultrasonographically proved nephrocalcinosis with normal renal function.

Analysing the possible causes of calcium deposition in the kidneys, we found a significant difference in the daily phosphate intake and excretion between the nephrocalcinosis group and those with normal renal ultrasonography. The average calcium excretion did not differ between the two groups. The incidence of hypercalciuric episodes was higher in the nephrocalcinosis group, in which all patients had at least one episode of hypercalciuria (table 2). One patient with nephrocalcinosis had episodes of mild hypercalcaemia, while in the group without nephrocalcinosis only one single episode of hypercalcaemia occurred. Goodyear *et al*[18] put forward the hypothesis that increased calcium excretion was thus related to nephrocalcinosis.

In patients with idiopathic renal hypercalciuria the most common finding is recurrent renal stone formation and not nephrocalcinosis. In both the study of Goodyear *et al* and ours no clinical signs of nephrolithiasis were detected. Hypercalciuric patients had, however, constantly increased calcium excretion, whereas in X linked hypophosphataemia hypercalciuria is not a constant state; it was found in only about 10% of the collected urine specimens.

The high phosphate excretion constitutes another important difference between this group of patients and patients with hypercalciuria. Thus in patients with X linked hypophosphataemia the renal collecting ducts are filled continuously and the renal papillae are bathed in a fluid with a high concentration of phosphate. If hypercalciuria then occurs crystallisation will build up.

High phosphate intake may also cause secondary hyperoxaluria. In a recent study we showed a close association between the relative daily dose of phosphate and urinary oxalate excretion in patients with X linked hypophosphataemia.[21] The mechanism could be explained by the binding of calcium in the intestine and consequent hyperabsorption of oxalate.

Urinary calcium excretion of less than even the 0·1 mmol/kg/day limit could contribute to calcification according to the principles of complex equilibria, if other constituents of relatively insoluble calcium salts are present in excess.[19 20]

The spontaneous urine output of patients with X linked hypophosphataemia during periods of hypercalciuria did not differ substantially from that of the control group. This could be taken to indicate the absence of overt hypercalcaemia, but on the other hand absolute excretion of crystalloids is second only to urine volume as the other factor determining urine concentration and saturation. Thus patients with X linked hypophosphataemia—if treated with phosphate and vitamin D analogues—should be encouraged to drink large amounts of fluid and to avoid dehydration. Urinary calcium and phosphate excretion, and the concentration of other potential lithogenic substances should be studied to elucidate further the mechanism of renal calcium deposition in this group of patients.

The lack of correlation between high doses of phosphate and the change in height SD scores means that children receiving higher oral doses of phosphate do not necessarily grow better than patients on lower daily doses of 50–100 mg/kg phosphate. In this group with normal renal ultrasonography similar height was achieved without the risk of nephrocalcinosis.

In the light of the data on growth and on the side effects of treatment an even more careful evaluation of the individual data of patients is certainly indicated, but we do not see that the suggested discontinuation of the treatment of patients with X linked hypophosphataemia is justified.[15]

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Reappraisal of thyroxine treatment in primary hypothyroidism

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Abstract

The optimum daily dose of thyroxine was calculated for 13 children aged 3–16 years with primary hypothyroidism by titrating their doses at monthly intervals. The condition of the thyroid was assessed by sensitive assay of thyroid stimulating hormone concentrations, as well as measurement of total and free thyroid hormone concentrations and systolic time interval ratios. Serum thyroid stimulating hormone concentration was found to be the most responsive to small changes in thyroxine. The calculated optimum daily replacement dose of thyroxine (102 $\mu g/m^2$ or 3·5 μg/kg) was fractionally lower than that previously recommended, and was more closely related to surface area (coefficient of variation 8·2%) than to body weight (coefficient of variation 16.2%).

Our results suggest that though monthly may be the optimal time interval for increases in the dose of thyroxine, any reduction in the dose should be made more gradually.

Neonatal screening for congenital hypothyroidism together with adequate treatment should allow normal physical and intellectual development. For optimal results careful adjustment of the dose of thyroxine according to age and body size is necessary. An inadequate dose may affect intellectual and neurological development adversely,[1] whereas excessive replacement may lead to craniostenosis,[2 3] advanced bone age, and hyperactivity.[4] In 1979 Rezvani and Di George suggested a daily dose of 105 $\mu g/m^2$, or 3·8 μg/kg for hypothyroid children aged more than 1 year; this was significantly less than the previously recommended doses. Several subsequent developments, paticularly the 11% increase in bioavailable thyroxine content of the British Pharmaceutical Codex formulation (*British Pharmacopoeia 1980*), the introduction of 25 μg tablets in the same year, and the advent of sensitive immunoradiometric assays (IRMA) for the measurement of serum thyroid stimulating hormone concentrations have justified a reappraisal of the optimal doses of thyroxine for hypothyroid children.

After the introduction of the highly sensitive thyroid stimulating hormone IRMA we became concerned that a number of children in the clinic had unmeasurably low concentrations, and thus could be considered to be over treated. The aim of this study, therefore, was to determine the 'optimal' dose of thyroxine, defining this as the minimal dose at which the thyroid stimulating hormone was suppressed sufficiently to come within the reference range. We have also tried to determine whether the systolic time interval ratio (pre-ejection period:left ventricular ejection time), which has been established as a reliable measure of end organ response to thyroid hormones in adults,[6 7] could be used as a physiological marker of adequacy of replacement in children.

Patients and methods

Fifteen patients with previously diagnosed primary hypothyroidism were investigated. Informed parental consent was obtained and the study was approved by the local ethics committee.

Thirteen children (nine girls and four boys) aged between 3 and 16 years (mean age 10·3) completed the study. Seven had congenital hypothyroidism and six had juvenile hypothyroidism. Nine of the 13 children were prepubertal. The children were seen at monthly intervals. At the initial visit the weight, height, and dose of thyroxine were recorded and bone age was estimated by the method of Greulich and Pyle.[8] A blood sample was taken by venepuncture and the serum was divided into two aliquots. In one aliquot thyroid stimulating hormone (Boots Celltech IRMA) was estimated with seven days as a guide to dose adjustment. The second was stored at −20°C until the end of the study when all the serum samples of each patient were assayed for free triiodothyroxine (T_3) (Immunodiagnostics Ltd) (reference range 3·6–7·8 pmol/l), free thyroxine (T_4) (Clinical Assays 2 stage, Baxter Health Care) (reference range 7·7–20·6 pmol/l), and thyroid stimulating hormone again, in their respective single assay runs. If the initial thyroid stimulating hormone concentration was within the reference range (0·3–4 mU/l) (n=12) the dose of thyroxine was reduced by 12·5 μg at monthly intervals until the thyroid stimulating hormone concentration rose above 4 mU/l. The dose was then increased by 12·5 μg at monthly intervals until the thyroid stimulating hormone concentration was again within the reference range.

If the serum thyroid stimulating hormone concentration was initially raised (>4 mU/l) (n=1) the dose of thyroxine was increased at monthly intervals until it returned to the reference range.

Data are presented for four time points: point 1, entry to the study; point 2, the last reduction in dose that kept the thyroid stimulating hormone concentration within the reference range; point 3, the dose at which the thyroid stimulating hormone concentration rose above the refer-

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ence range; and point 4, the point during the incremental dose adjustment at which the thyroid stimulating hormone concentration returned to the reference range.

At each clinic attendance pre-ejection period and left ventricular ejection times were measured according to a previously reported technique,[9] and the systolic time interval ratio was calculated. The systolic time intervals were also calculated for 43 euthyroid children between the ages of 3 and 16 years to provide a reference range for the age group under study.

Patients were asked about symptoms suggestive of over replacement and under replacement at each attendance. Thyroxine was dispensed by the hospital pharmacy as 25 μg or 50 μg tablets and these were specially packed in accordance with the monthly titration requirements of the study. Detailed instructions were given to the parents. Tablets were counted at the beginning and end of each study period to assess compliance.

The significance of differences were assessed by the paired *t* test for all data except thyroid stimulating hormone concentrations. These were no normally distributed and therefore the Wilcoxon test was used.

Results

The association between the thyroxine dose given (μg/m^2/day) and the thyroid stimulating hormone concentration at each time point is shown in fig 1. At entry (time point 1) thyroid stimulating hormone was in the lower part of the reference range for the group as a whole, but moved higher during downward titration of the dose of thyroxine (time point 2). Further downward titration (until the thyroid stimulating hormone for each individual patient rose above the reference range point 3) was followed by upward titration to suppress the thyroid stimulting hormone of each patient until it was within the reference range (point 4). The thyroxine dose at point 2 (91·5 μg/m^2) was significantly lower than at point 4 (102·2 μg/m^2, $p<0·005$) despite the similarity in thyroid stimulating hormone concentrations at these two points. Figure 2 shows that there was no significant difference at points 2 and 4 either in free triiodothyronine (6·4 compared with 6·3 pmol/l, $p=0·34$) or free thyroxine (24·6 compared with 24·5 pmol/l, $p=0·99$).

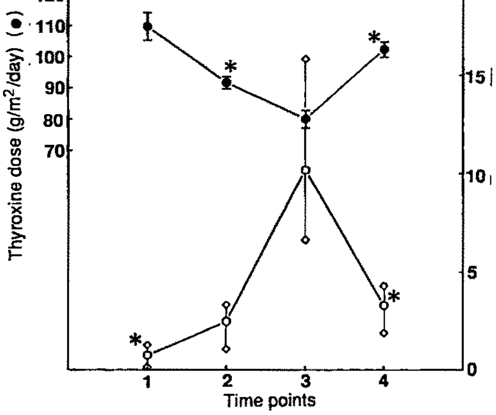

Figure 1 Thyroxine dose (μg/m^2/day) and concentration of thyroid stimulating hormone (mU/l) at each of the four time points of the study. ($p<0·005$). Dose of thyroxine is expressed as mean (SEM) and concentration of thyroid stimulating hormone as median (interquartile range).*

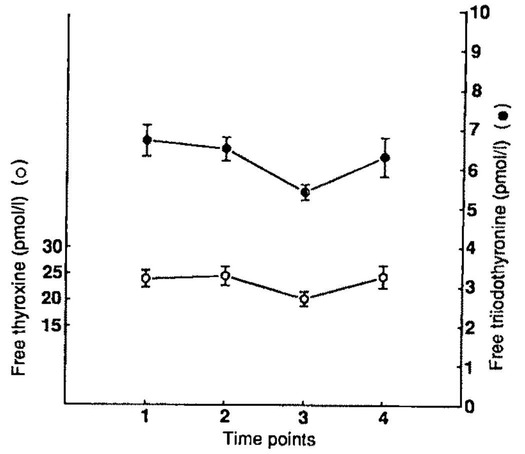

Figure 2 Free triiodothyronine (solid circles) and free thyroxine (open circles) concentrations at the four time points expressed as mean (SEM).

The final dose of thyroxine reached by upward titration until the thyroid stimulating hormone came within the reference range (point 4) was not significantly different from that at entry (102·2 μg/m^2 compared with 109·6 μg/m^2, $p=0·16$). The thyroid stimulating hormone concentration was, however, significantly lower at point 1 than at point 4 (0·74 compared with 3·30 mU/l, $p<0·005$), although neither free triiodothyronine nor free thyroxine concentrations differed significantly at points 1 and 4 ($p=0·45$ and 0·83, respectively).

Figure 3 shows the measurements of systolic time interval of the study group at each time point in relation to the 80% prediction band calculated using the results from the group of 43 euthyroid children. One measurement is missing from time points 2–4. The observed systolic time intervals at time points 1 and 4 were indistinguishable from those of the euthyroid population. At both time points 2 and 3, however, in a third of the study group the systolic time intervals were clearly outside the 80% prediction band, and two older children had unequivocally hypothyroid values.

The precision of estimating the thyroxine dose by body weight or surface area was compared by calculating coefficients of variation for these two measures at thyroid stimulating hormone euthyroidism (points 2 and 4 pooled). The coefficient of variation was 8·2% for the dose expressed by m^2 and 16·2% when expressed by kg body weight. The regression of dose by surface area at time point 4 is shown in fig 4.

When juvenile and congenital hypothyroid patients were considered separately, results did not differ appreciably.

At entry to the study two patients had symptoms suggestive of hyperthyroidism (over activity and poor sleeping). Two girls were withdrawn; one with Hashimoto's thyroiditis complained of pain and swelling of her thyroid

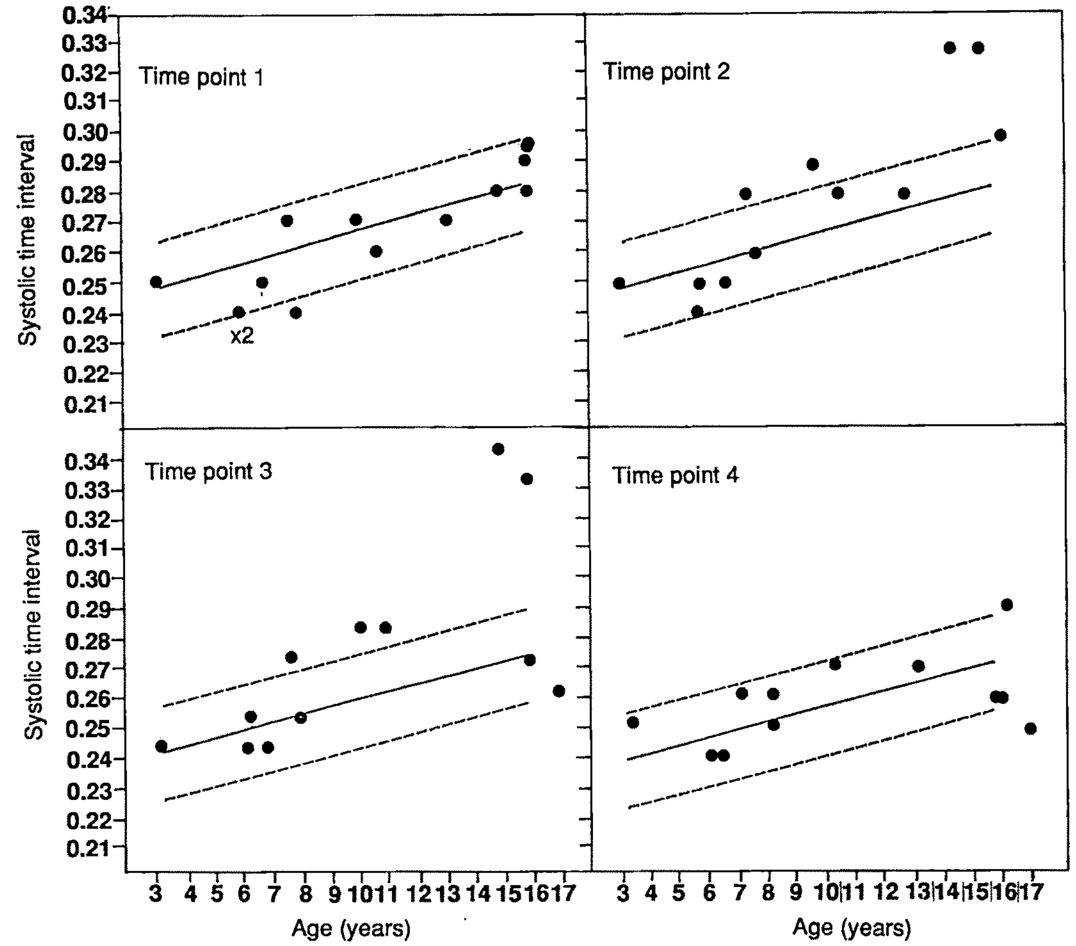

Figure 3 · Systolic time intervals for each patient at the four time points. The regression line of systolic time interval on age (solid line) and its 80% prediction band (interrupted lines) for euthyroid children are shown.

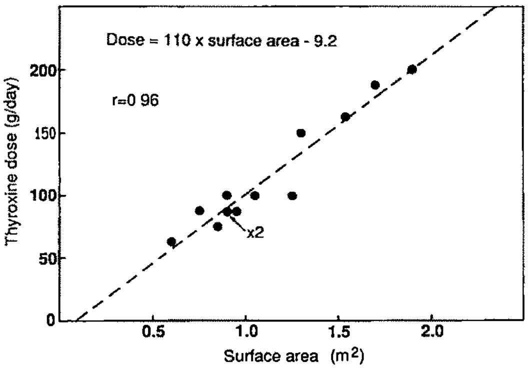

Figure 4 The relation between thyroxine dose (µg/day) and body surface area (metre²) at time point 4 with the calculated regression equation and correlation coefficient.

gland when her dose of thyroxine was reduced although she remained biochemically euthyroid, and the other remained clinically and biochemically euthyroid after she had stopped taking thyroxine. At the end of the study all patients were free of symptoms and six of the study group were receiving smaller doses of thyroxine than they had been at entry.

Discussion

We have shown that in children with primary hypothyroidism the optimal daily dose of thyroxine defined as the minimum dose that suppresses the serum thyroid stimulating hormone until it is with the reference range, and determined with 12·5 µg increments of thyroxine, is 102 µg/m² (or 3·5 µg/kg). This is fractionally lower than that previously recommended. Dosage requirements correlated better with surface area than body weight. Judging by measurements of systolic time interval, the children's cardiac tissue did not show evidence of over treatment at the time of inclusion in the study when compared with age matched controls in spite of their free thyroid hormone concentrations being at the upper limit of the adult reference range. Considering the group as a whole there were no consistent alterations in systolic time interval during titration of the dose of thyroxine, although about a third of the subjects developed hypothyroid values at the time of the raised serum thryroid stimulating hormone concentrations. The design of the study, in which doses were titrated downwards as well as upwards, has highlighted an interesting discrepancy. Lower optimal doses were arrived at during downward compared with upward titration even though thyroxine and triiodothyronine concentrations were similar at the respective optimal end points. This might be explained by the fact that a 28 day titration period is too short for adequate dose reduction. The serum half life of thyroxine is roughly six days[10] and, if five times the half life is required to reach a steady state plasma concentration, there may still be some contribution to plasma concentrations from the immediately previous higher dose of thyroxine.

In contrast, a monthly interval between increments is sufficient to produce maximal thyroid stimulating hormone suppression during upward titration in adults.[11] Sato *et al* showed that children with congenital hypothyroidism who were studied between 6 months and 17 years of age required unusually large doses of thyroxine/kg body weight to block their thyroid stimulating hormone response to thyrotrophin releasing hormone.[12] More recently, Schultz *et al* described five infants with congenital hypothyroidism who had persistently raised serum thyroid stimulating hormone concentrations after being given thyroxine in doses that would usually be considered adequate.[13] These observations suggest that congenitally hypothyroid children have a particularly high threshold for thyroid stimulating hormone suppression by thyroxine. It could be argued that in our study the attainment of over suppressed thyroid stimulating hormone concentrations (as shown by the lower concentrations on admission to the study) after long term administration of similar doses of thyroxine to those which, during the study, lowered thyroid stimulating hormone just into the reference range supports the hypothesis of an initial high threshold for thyroid stimulating hormone suppression. Moreover, the pronounced rise in thyroid stimulating hormone seen in our subjects after a 12·5 μg decrement of thyroxine (fig 1) raises the possibility that this increased threshold is the consequence of the driving effect of thyrotrophin releasing hormone on thyroid stimulating hormone release.

The discrepancy in dose requirements that we have identified is of some importance when reviewing previous reports. For instance, Rezvani and Di George suggested an optimal dose of 105 $\mu g/m^2$ during downward titration, but this is likely to have been an under estimate of the dose required to produce thyroid stimulating hormone suppression during upward titration should they have adopted such.[5]

In adults the systolic time interval ratio is a reliable monitor of peripheral thyroid hormone activity.[6 7] The systolic time intervals obtained in this study at the time of entry did not suggest that the children were over treated. It is likely that the variability of the systolic time interval with age (as observed in the control group) and the problems of achieving a resting state in young children limit the clinical usefulness of the systolic time interval ratio as an index of peripheral thyroid hormone activity in children.

We conclude that, in children with primary hypothyroidism, the optimal daily dose of thyroxine when prescribed in the current British Pharmaceutical Codex formulation, is slightly lower than previously recommended. The required dose correlates more closely with surface area than with body weight. Assay of thyroid stimulating hormone by IRMA provides a sensitive means of monitoring even minor dose adjustments, whereas the 'tissue marker', the systolic time interval, is less sensitive. The discrepancies between incremental and decremental titration may be of clinical relevance in that though the time interval of one month may be adequate between increments, it may be necessary to decrease thyroxine more gradually in children with over replacement if under replacement is to be avoided.

We thank the pharmacy department, Leicester Royal Infirmary, for packaging and dispensing the thyroxine.

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Survey of adolescents with severe intellectual handicap

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Abstract

A diagnostic survey was undertaken of children aged 11 to 19 years in Tameside with severe learning difficulties (intelligence quotient ≤50). Eighty two children were identified and their medical records reviewed. A specific diagnosis for the retardation was documented in 25 (30%) of the children, 18 of whom had Down's syndrome. A probable aetiology or a disorder of unknown aetiology had been identified in a further 21 (26%) children. To confirm the existing diagnosis, identify new diagnoses, and offer genetic counselling, the parents of 63 children were offered detailed reassessment of their child. Fifty three children were reviewed, and a specific disorder identified in 25 out of 31 previously undiagnosed children. The most frequent diagnoses made were fragile X syndrome and Rett's syndrome. On completion of the survey, 61 of the 82 children (74%) had a specific diagnosis or probable aetiology identified, 12 (15%) had associated disorders such as cerebral palsy, and in only nine of the 82 children (11%) were there no clues at all to the cause of their retardation.

Severe mental retardation occurs with a prevalence of approximately 3–4/1000 of the general population. It is not always possible to identify a specific aetiology for severe mental retardation, but it is important to reach a diagnosis wherever possible as this enables information to be given to parents about the cause and ultimate prognosis for their child's disorder, as well as determining recurrence risks for future children of the parents and other relatives. Reassessment of affected individuals is important as new disorders associated with mental retardation are identified, and improved cytogenetic techniques enable the detection of subtle structural chromosomal abnormalities such as interstitial deletions.

Surveys of severely retarded individuals (intelligence quotient (IQ) ≤50) undertaken before the identification and description of the fragile X syndrome documented a defined cause for the retardation in approximately 50% of cases.[1–3] More recent surveys of severely retarded institutionalised patients have demonstrated a defined disorder or aetiology in 82–88% of cases.[4 5]

The excess of affected males with non-specific mental retardation has been recognised for many years, and Rosanoff (1931)[6] and Penrose (1938)[7] suggested X linked recessive inheritance as a major cause of mental deficiency. The fragile X chromosome was first demonstrated by Lubs in 1969,[8] and its folic acid dependent expression and association with mental retardation reported in 1977.[9 10] The definition of the clinical syndrome during the late 1970s and early 1980s is summarised by Fryns.[11] This disorder is now thought to be the second most common cause of mental retardation after Down's syndrome, with an estimated prevalence of 0·3–1/1000 males and 0·2–0·6/1000 females.[12–14] Identification of this inherited disorder in retarded children is important because of the genetic implications. Many aspects of the condition are not understood, however,[15] including transmission by apparently unaffected males, and the high proportion of heterozygous females who have some intellectual impairment usually of mild to moderate degree.

The present study initiated by one of the authors (JCA) was undertaken to identify severely retarded children with fragile X syndrome in the Tameside borough, and where possible to reach a diagnosis in other children with previously unexplained severe retardation, so that families could be offered genetic counselling.

Patients and methods

The study population was drawn from children aged 11 to 19 years attending special schools in Tameside for children with severe intellectual handicap (IQ ≤50). At the start of the study the estimated total school population aged 11 to 19 years in Tameside was 27 585 (13 851 boys, 13 734 girls), and all children with severe retardation of this age in the borough received special education at one of two special schools. Eighty two severely retarded children were identified, giving a prevalence of 3/1000 population in Tameside, which is comparable with the general population prevalence, and probably represents fairly complete ascertainment of severe mental retardation in the borough.

The secondary school age group was chosen because children with intellectual handicap under the age of 11 years in Tameside have all been assessed by a multidisciplinary team at the child development unit, and have been fully investigated. The older children had all been assessed in early childhood by a paediatrician before the child development unit was established, and details of prenatal and postnatal histories and early childhood development were well documented. Not all of these children were attending hospital based follow up clinics, however, as their general health was good and their retardation non-progressive. They had not

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had recent detailed re-evaluation, although they all received annual medical examinations at school by a senior clinical medical officer.

Of the 82 children identified with severe retardation, 18 had Down's syndrome (14 boys, four girls) and one had suffered a severe head injury in a road traffic accident. These children were excluded from detailed review as there was no doubt about the aetiology of their retardation. The parents of the remaining 63 children were asked whether they wished to have a detailed reassessment of their child performed jointly by the school senior clinical medical officer, a clinical geneticist, and a paediatrician. The reassessment included taking a history covering the pregnancy and perinatal period, early childhood development, and the general health of the child. The family pedigree with all relevant details was documented, and a full physical examination of the child undertaken, with particular attention paid to clinical measurements, dysmorphic features, or abnormal neurological signs. Further investigations were done when clinically indicated, including screening for fragile X syndrome in children without dysmorphic features in whom no other aetiology or diagnosis was apparent.

All the cytogenetic analyses were performed by one of the authors (JSH). Three 72 hour lymphocyte cultures were set up from each sample for fragile X studies, using 0·5 ml of whole blood and 4 ml of medium. The first culture used Roswell Park Memorial Institute 1640 medium with penicillin/streptomycin, glutamine, and 20% fetal calf serum. Thymidine was added to a final concentration of 380 mg/l 22 hours before harvest, and this block was released five hours before harvest with 2-deoxycytidine (2·28 mg/l). The second culture was set up under the same conditions but the thymidine block was not released. The third culture used 199+Hepes medium with penicillin/streptomycin, glutamine, and 5% fetal calf serum. A total of 100 mitoses were analysed in boys and 150 in girls.

Table 1 Diagnostic classification of 82 severely retarded children obtained from previous hospital records

Classification	*Boys*	*Girls*	*Total*
Diagnosed disorder:			
Down's syndrome	14	4	18
Head injury (road traffic accident)	1	0	1
Tuberous sclerosis	2	0	2
Williams syndrome	0	1	1
Fanconi's syndrome	1	0	1
Angelman's syndrome	0	1	1
Congenital toxoplasmosis	1	0	1
(Subtotal)	(19)	(6)	(25)
Probable aetiology identified:			
Agenesis corpus callosum	0	1	1
Birth asphyxia	0	4	4
Cyanotic heart disease	1	0	1
Subdural haematoma	0	1	1
Prolonged febrile convulsions	1	0	1
Hypernatraemic dehydration	0	1	1
(Subtotal)	(2)	(7)	(9)
Disorder of unknown aetiology:			
Cerebral palsy	0	2	2
Epilepsy	2	2	4
Dysmorphic syndrome	4	0	4
Autism	1	1	2
(Subtotal)	(7)	(5)	(12)
Unidentified disorder	20	16	36
Total	48	34	82

Table 2 Diagnoses made during the survey in 25 of 31 previously unclassified children

Diagnosis	*Boys*	*Girls*	*Total*
Fragile X syndrome	11	4	15
Rett's syndrome	0	5	5
Chromosomal abnormality	1	0	1
Angelman's syndrome	0	2	2
Congenital myotonic dystrophy	1	0	1
Behr's syndrome	1	0	1
Total	14	11	25

The parents of 10 children requested no reassessment or failed to reply, and 53 children were therefore seen during the survey.

Results

The existing diagnoses or identified aetiologies shown in table 1 were confirmed during the survey. New diagnoses reached in 25 cases are listed in table 2.

During the survey chromosome cultures for fragile X studies were done in 15 boys and 11 girls. Positive results were found in 11 boys (3–45% positive cells) and four girls (4–6% positive cells). Not all of these children had the physical characteristics of the syndrome, although seven boys and one girl did have large jaws, large ears, or prominent foreheads. The 15 children diagnosed came from 12 families, with three pairs of affected siblings being identified in the study population: two sets of brothers and one brother and sister. In two families there was a previous family history of mental retardation suggesting an X linked recessive pattern of inheritance. In the remaining seven families the retarded child was the only affected person in the family.

All the mothers of the affected children identified agreed to have fragile X studies performed on themselves. Seven out of eight mothers of the affected boys were fragile X positive (2–14% positive cells), and two of these women had a low IQ. The mothers of the four isolated affected girls were all fragile X negative and had normal IQs. One obligate carrier, with an affected son and two affected daughters, did not demonstrate the fragile X chromosome on analysis.

Ten sisters of affected probands were tested. Two were fragile X positive, of whom one had a low IQ. Eight were fragile X negative, of whom two had a low IQ. Seven out of 15 maternally related aunts and cousins potentially at risk have so far been tested, and all were fragile X negative. DNA analysis using linked restriction fragment length polymorphisms is currently being performed in families of suitable structure.

Standard chromosome analysis was performed in 17 children in addition to those found to be fragile X positive. One boy who had no dysmorphic features was found to have extra unidentified chromosomal material attached to the short arm of one chromosome 12 (46,XY,(12p+)). No chromosomal abnormalities were detected in the other 16 cases, including three boys with multiple congenital abnormalities. Literature review together with a syndrome data base search failed to show a definitive diagnosis in these boys.[16] Chromosome 15q deletions were not detected in the two girls with clinically diagnosed Angelman's syndrome from whom samples could be obtained.

Five girls were diagnosed as having Rett's syndrome. All had been born at full term after normal pregnancies and there were no perinatal problems apart from mild and transient feeding difficulties in four. Developmental regression was documented in all five girls, starting between the ages of 6 and 18 months. In two girls the regression had previously been attributed by the parents to whooping cough vaccination, and in another to a relatively mild episode of gastroenteritis. Normal head circumference at birth with subsequent microcephaly was documented in all five girls. All had typical stereotyped hand movements, and none had useful manipulation skills. Two girls had never been able to walk, the other three had an unsteady gait but were ambulant with help. All five girls had abnormal recordings on electroencephalography and clinical epilepsy, which had become easier to control in three girls from the ages of 8, 9, and 16 years respectively. Scoliosis of varying degree was present in four, and four had poor peripheral circulation. All the girls had increased limb tone, brisk reflexes, and periods of hyperventilation. One girl required oxygen treatment and was too ill to attend school. She died from respiratory failure during the course of the survey. No biochemical abnormalities were detected in any of the girls, and computed tomography of the brain performed in one showed no structural abnormality of the central nervous system. Family history was negative in all five cases.

One case of Behr's syndrome (inherited spinocerebellar degeneration with posterior column loss, optic atrophy, and mental retardation) and another of congenital myotonic dystrophy were identified during the survey, and the diagnosis confirmed on referral to neurology clinics.

Perinatal and postnatal factors previously thought to have been implicated in the mental retardation in six cases were confirmed. These included three children with severe birth asphyxia, one child a subdural haematoma occurring at 3 months of age, another with hypernatraemic dehydration and convulsions during a severe gastroenteritic illness, and one child with a febrile convulsion lasting over an hour and a half at the age of 2 years.

No diagnosis was reached in eight of the children reviewed. These children included two with epilepsy, one of whom had moderately retarded parents. There was no positive family history in the remaining six children.

The case notes of the 10 children whose parents declined reassessment were reviewed, and showed no identifiable aetiology in three. Two of the children were brothers, suggesting a genetic aetiology, and they did have clinical features compatible with the fragile X phenotype. Among the remaining five, there was probable birth asphyxia in one, severe cyanotic heart disease and Eisenmenger's syndrome in one, dysmorphic features and parental consanguinity in one, and epilepsy in two of whom one child was autistic and the other had moderately retarded relatives.

At the end of the survey a diagnosis or probable aetiology could be identified for 61 of the 82 children (74%). In a further 12 children (15%) there were associated disorders such as cerebral palsy, epilepsy, autism, or congenital abnormalities of unknown aetiology. The retardation remained completely unexplained in nine (11%) children (four boys, five girls).

Discussion

During the study period, a diagnosis was made in 25 out of 31 children in whom there had previously been no aetiology identified for their retardation. As expected from reports of other school surveys,[17 18] fragile X syndrome was the most frequently diagnosed disorder.

Establishing a diagnosis enabled genetic information to be given to the families, many of whom had children or other relatives reaching reproductive age who were concerned about risks of recurrence. The genetic implications for relatives are particularly important when a diagnosis of fragile X syndrome is made. During this survey, apart from one family where the affected boy's mother did not wish to inform her sisters and nieces of the diagnosis, the relatives of children with fragile X syndromes all took up the offer of genetic counselling and further investigation. Most female relatives at, or reaching, reproductive age who were potentially at risk felt that they would wish to avail themselves of prenatal diagnosis in the future.

The prevalence of fragile X syndrome in severely retarded children in Tameside estimated from this survey is 0·8/1000 boys and 0·3/1000 girls. Children with mild to moderate learning difficulties (IQ 50–70) were not reviewed, and this group of children in Tameside may contain further cases of fragile X syndrome, particularly girls, although this disorder has not always been identified in surveys of children with mild to moderate disability.[19]

In contrast to fragile X syndrome, other chromosomal abnormalities, which may be found more commonly in children with mild mental retardation,[20] were detected in only one case in the present survey.

The diagnosis of Rett's syndrome in five girls gives a prevalence in Tameside of 3·6/10 000 girls. This is considerably higher than the estimated prevalence of 0·8/10 000 girls up to the age of 14 years that has been previously reported.[20–23] Rett's syndrome was first described in 1966,[24] and to date no biochemical or chromosomal abnormality has been consistently found in affected girls. Confirmation of the diagnosis will be important when the underlying biochemical or genetic defect is defined. The five girls in the present survey did fulfil all the diagnostic criteria for Rett's syndrome delineated during the 1986 workshop on the disorder,[25–27] and summarised by Hagberg.[28] These clinical features include female sex and a normal prenatal and perinatal period with early normal development. This is followed by deterioration and loss of skills, normal head circumference at birth with deceleration of head growth in early childhood, loss of purposeful hand skill, development of hand ringing and clapping stereotypes, and appearance of gait and truncal apraxia by the age of 4 years. Four clinical stages in classical Rett's syndrome have been described, and the girls in this survey corresponded to stages III and IV, representing a severe multihandicap syndrome with decreasing mobility, scoliosis, and the development of paraplegic or tetraplegic signs. Familial recurrence of Rett's syndrome is infrequently reported,[28 29] and low recurrence risks are generally quoted. There were no positive family histories in any of the five girls identified during this survey.

In nine children in this survey population there were no clues to the underlying diagnosis or cause of their retardation. Precise calculation of recurrence risks to use when counselling relatives of these children is difficult. Figures are generally based on reported recurrence risks of between 2–10% observed in siblings in previous studies of severe non-specific retardation.[30–36] These surveys report an excess of male cases, and higher recurrence risks when the proband is male, probably influenced by the inclusion of some undiagnosed families with fragile X syndrome, as well as cases of non-specific X linked mental retardation.

The results of the present survey indicate that reassessment of severely retarded children without a diagnosis is of value, and should be considered as part of the regular medical review of children attending special schools. The majority of parents appreciated the review and the chance to discuss their child's problems at length, even when no diagnosis could ultimately be offered. Although most parents had completed their own families, genetic counselling was appropriate as siblings and other relatives were reaching reproductive age.

We wish to thank all the parents who cooperated with this survey, and are grateful to Vera Hobson, community nursing sister, and the staff of Cromwell and Oakdale Special Schools for their help in arranging the medical reviews of the children.

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Normal small bowel biopsy followed by coeliac disease

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Abstract

We report four patients (two children, one adolescent, and one adult) having normal small bowel mucosa shown on a biopsy specimen taken before the initial diagnosis of coeliac disease was made. The first biopsy was undertaken in two cases because of suspected malabsorption, in the third because of suspected dermatitis herpetiformis, and in the fourth as part of a coeliac disease family study. After a further 2·6 to 9 years on a diet containing gluten, small bowel villous atrophy with crypt hyperplasia compatible with coeliac disease was found on a second biopsy specimen. The HLA type of the patients was that typical for coeliac disease; all were DR3 positive. Within the families three other patients with coeliac disease have been diagnosed, two earlier and one at the time the first biopsy was undertaken. Four other HLA-DR3 positive haploidentical first degree relatives were found and had biopsies. All four had normal small bowel villous architecture, one had an increased intraepithelial cell count, and another was positive for reticulin and endomysium antibodies. Coeliac disease may exist latent in patients having normal mucosa when eating a normal diet containing gluten.

It is generally accepted that a normal small bowel biopsy specimen, taken for the first time when the patient is eating a normal diet containing gluten, rules out the diagnosis of coeliac disease once and for all. At present we demand an abnormal small intestinal mucosa (subtotal villous atrophy or flat mucosa) as being essential for a diagnosis of coeliac disease. There are several observations, however, for example, late relapsers on gluten challenge[1] (I Polanco, J Larrauri. Abstract presented at the International Coeliac symposium, St Bartholomew's Hospital, London, 4–6 September, 1988) and late appearing concordancy in monozygotic twins,[2 3] indicating that coeliac disease may exist latent in patients having normal mucosa when eating a normal diet. There are few such patients described in the literature.[4–6] We now report four patients in whom the first biopsy specimen ruled out coeliac disease but who were later found to have the disease. The patients were HLA typed and family members were also studied in greater detail.

Methods

Information on symptoms and signs compatible with coeliac disease was obtained by parental and patient recall and also by reviewing the hospital medical records.

Routine small bowel biopsy was performed with a paediatric or adult Watson capsule and the specimens were studied under light microscopy.

Serum IgA and IgG class gliadin[7] and reticulin[8] as well as IgA class endomysium[9] antibodies were studied as earlier described.

Serological HLA typing of the patients and also of the family members for A, B, C, and DR locus antigens was performed[10] and DR typing confirmed by restriction fragment length polymorphism from DNA samples using Taq I restriction enzyme and DR β probe from the X International Histocompatibility Workshop.[11]

Results

CASE REPORTS

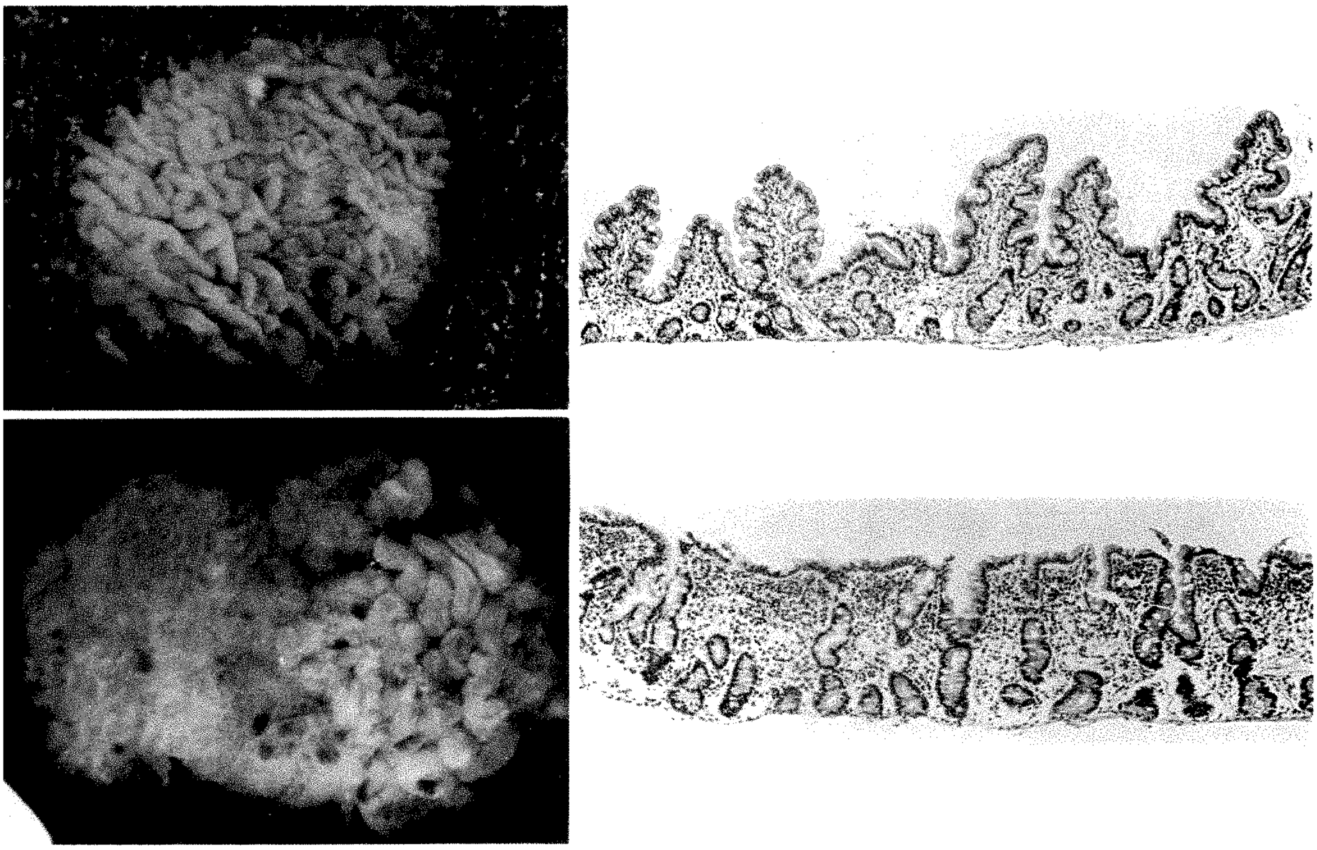
Case 1

This girl was referred to the hospital at 0·9 years of age on account of poor weight gain. She had

Table 1 Case 1: clinical data and results of serum antibody studies and small bowel biopsy

	Referral	*Follow up*					
Age (years)	0·9	1·2	2·2	3·5†	3·8	4·5	5·4
Gluten in diet	Yes	Yes	Yes	Yes	No	No	No
Abdominal symptoms	No	No	No	No	No	No	No
Height (SD)	−0·5	−0·5	−0·5	−0·5	−0·5	−0·5	−0·5
Weight (SD)	−1·0	−1·0	−0·5	−0·5	−0·5	−0·5	−0·5
Gliadin antibodies*							
IgA	0·12	0·05	<0·05	0·78	0·09	<0·05	<0·05
IgG	9·80	3·32	1·97	37·00	5·30	0·28	0·35
Reticulin antibodies*							
IgA	Negative	Negative	Negative	1:500	Negative	Negative	Negative
IgG	Negative	Negative	Negative	Negative	Negative	Negative	NT
Endomysium antibodies*							
IgA	Negative	NT	NT	1:500	NT	NT	Negative
Biopsy	Normal			Subtotal villous atrophy			

*Reference values: gliadin antibodies (ELISA units/ml), IgA <0·2, IgG <5·0; reticulin antibodies, negative (serum titre <1:10); and endomysium antibodies, negative (serum titre <1:5).
NT=not tested.
†Gluten free diet started after this follow up.



igure 1 Dissection and findings on light microscopy of small intestinal mucosa of case 1 at the age of 0·9 years (upper figures) and at the age of 3·5 years lower figures). The patient had been on a normal diet containing gluten from the age of 5 months.

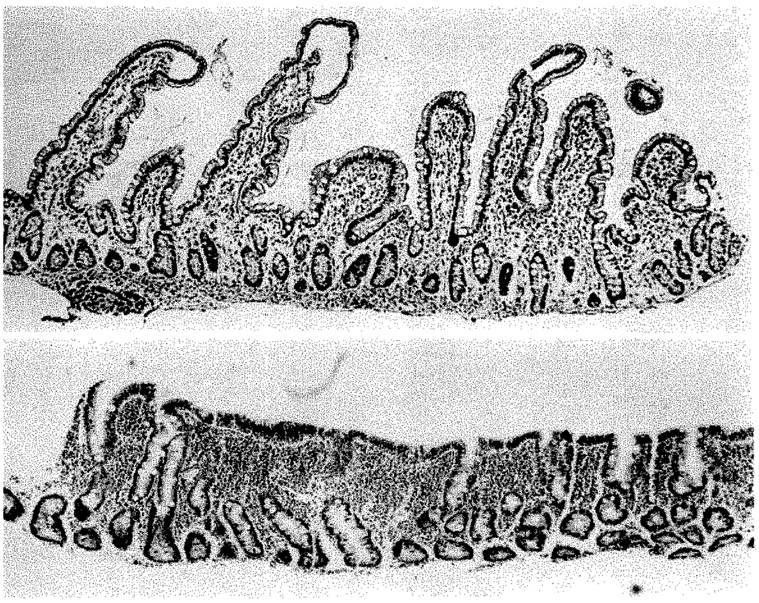
been breast fed for four months, and gluten had been introduced into her diet at 5 months of age. There was no family history of coeliac disease. She had had no abdominal symptoms and the stools were normal. Small bowel biopsy was performed because of slightly positive IgG class gliadin antibodies and poor weight gain (table 1). IgA class reticulin and endomysium antibody tests were at that time negative. In the upper part of fig 1 the dissection and light microscopic findings of the mucosa are shown. The biopsy specimen was interpreted as normal, excluding coeliac disease. On re-evaluation of the specimen the intraepithelial lymphocyte count was found to be 34/100 epithelial cells. She was followed up because of positive gliadin antibody titre. She gained weight on a diet containing gluten and the gliadin antibody titre decreased to negative values. The follow up was continued because of lack of growth and at the visit at 3·5 years of age both IgA and IgG class gliadin antibodies were positive. Also IgA class reticulin and endomysium antibody titres were high. The parents had noticed no change in her well being. A second biopsy specimen showed subtotal villous atrophy (fig 1, lower figures) with some patchiness seen in the dissection microscope. A gluten free diet resulted in the disappearance of gliadin, reticulin, and endomysium antibodies.

Case 2

Small bowel biopsy was performed on this boy at 2·3 years of age because of intermittent loose stools and because his brother had coeliac disease. His weight and height curves were normal. He was on a normal diet containing gluten. The biopsy specimen showed tall villous architecture and coeliac disease was excluded (fig 2). The intraepithelial lymphocyte count was 31/100 epithelial cells. IgA and IgG class reticulin antibodies were not detected. A coeliac disease family study showed at the age of 6·8 years a low IgA class reticulin antibody titre (1:10). Small bowel biopsy was not performed in view of the initial normal biopsy. On follow up at 7·6 years of age the IgA class reticulin antibody titre was 1:1000. He had experienced no abdominal symptoms. The second biopsy specimen showed subtotal villous atrophy (fig 2, lower figure). In table 2 serum gliadin and endomysium antibody results are also shown. After starting a gluten free diet the gliadin antibodies became normal (0·2 years) but IgA class reticulin and endomysium antibodies were positive, although lower.

Case 3

At 11·4 years of age this boy was suspected of having dermatitis herpetiformis because of his skin lesions. He was on a normal diet containing gluten as the other family members. He had no abdominal symptoms and his growth chart showed no deviations. At the same time his younger sister was studied because of short stature at 9 years of age and coeliac disease was diagnosed. Both skin and small bowel biopsies were performed. Reticulin antibodies were negative (table 3). Skin biopsy ruled out dermatitis herpetiformis and small bowel biopsy



igure 2 Small bowel mucosal architecture of case 2 at the age of 2·3 years (upper figure) nd 7·6 years (lower figure). He had been all the time on a normal diet containing gluten.

was thought to exclude coeliac disease irrespective of technical difficulties (fig 3). The intraepithelial lymphocyte count was at 21/100 epithelial cells. He passed puberty normally on a diet containing gluten. He was enrolled in a coeliac disease family study at 17·5 years of age and a second small bowel biopsy specimen showed subtotal villous atrophy (fig 3, lower figure). IgG class gliadin and IgA class both reticulin and endomysium antibodies were detected. Six months later on a gluten free diet reticulin and endomysium antibodies disappeared, and a control biopsy specimen showed considerable improvement of the villous architecture.

ble 2 Case 2: clinical data and results of serum antibody studies and small bowel biopsy

	Referral	*Follow up*		
e (years)	2·3	6·8	7·6†	7·8
iten in diet	Yes	Yes	Yes	No
dominal symptoms	Loose stools	None	None	None
owth	Normal	Normal	Normal	Normal
adin antibodies*				
gA	NT	0·07	1·35	0·10
gG	NT	10·10	21·00	1·45
iculin antibodies*				
gA	Negative	1:10	1:1000	1:100
gG	Negative	Negative	Negative	Negative
domysium antibodies*				
gA	NT	1:10	1:1000	1:100
psy	Normal		Subtotal villous atrophy	

eference values: gliadin antibodies (ELISA units/ml), IgA <0·2, IgG <5·0; reticulin antibodies, ative (serum titre <1:10); and endomysium antibodies, negative (serum titre <1:5).
=not tested.
uten free diet started after this follow up.

ble 3 Case 3: clinical data and results of serum antibody studies and small bowel biopsy

	Referral	*Follow up*	
e (years)	11·4	17·5†	18·0
iten in diet	Yes	Yes	No
owth	Normal	Normal	Normal
dominal symptoms	None	None	None
in biopsy (suspected dermatitis herpetiformis)	Normal	Normal	NT
adin antibodies*			
gA	NT	0·15	0·16
gG	NT	19·10	12·00
ticulin antibodies*			
gA	Negative	1:100	Negative
gG	Negative	Negative	Negative
domysium antibodies			
gA	NT	1:200	Negative
psy	Normal	Subtotal villous atrophy	Partial villous atrophy

eference values: gliadin antibodies (ELISA units/ml), IgA <0·2, IgG <5·0; reticulin antibodies, ative (serum titre <1:10); and endomysium antibodies, negative (serum titre <1:5).
=not tested.
luten free diet started after this follow up.

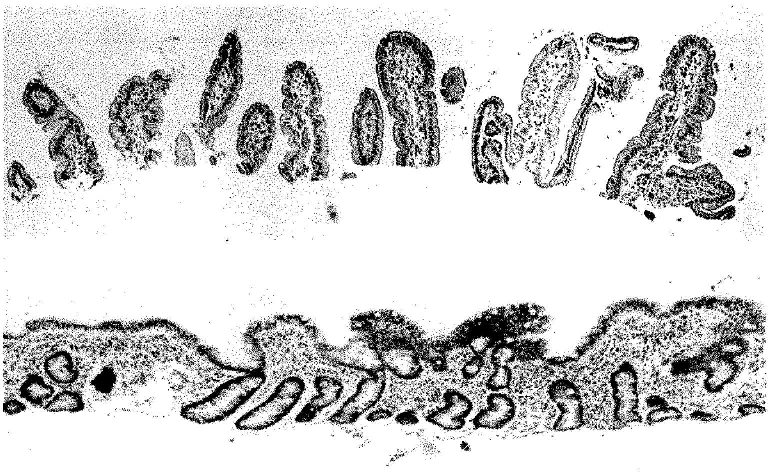
Case 4

At 32 years of age the patient was examined because of diarrhoea and suspected ulcerative colitis. She was on a normal diet containing gluten. She had a child with coeliac disease and was enrolled in a coeliac disease family study and found not to have coeliac disease because a small bowel biopsy specimen showed completely normal mucosa (fig 4). Nine years later another family study was performed that included small bowel biopsy. She did not mention that a biopsy had already been taken. She had no abdominal symptoms. Immunological tests were compatible with coeliac disease (table 4) and histologically her small bowel mucosa showed clear deterioration with partial villous atrophy with heavy plasma cell infiltration and a raised intraepithelial lymphocyte count at 41/100 epithelial cells (fig 4, lower figure). During dietary treatment serum antibodies became normal and a control biopsy specimen six months later showed considerable improvement with almost normal mucosa.

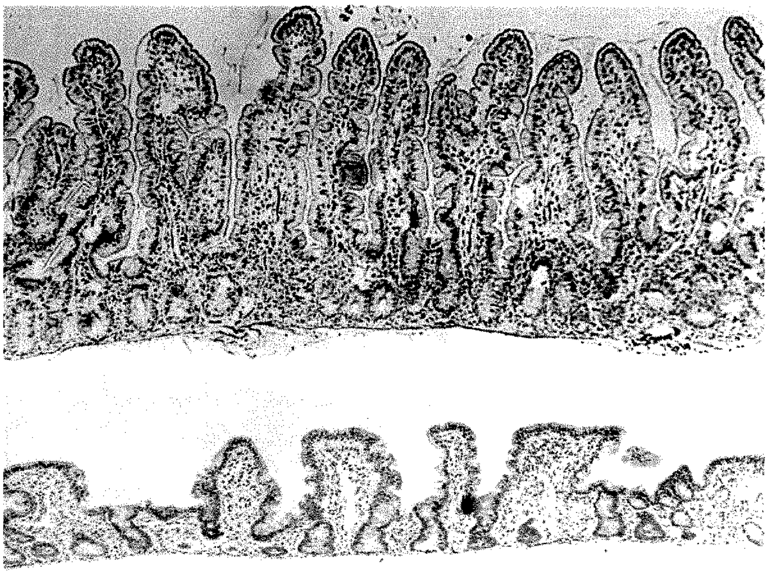
HLA RESULTS AND FAMILY MEMBER STUDIES

The results on HLA haplotypes of the patients and their family members are given in table 5. Each of the patients was positive for HLA-DR3. Two of the patients had HLA identical siblings suffering from coeliac disease and one patient had a HLA haploidentical son with the disease. Four other family members had the same HLA-DR3 positive haplotype as the patient. These four family members were on normal diets containing gluten but were also encouraged to eat normal food with at least 10 g of gluten per day for a further three months, after which they were studied for serum gliadin, reticulin, and endomysium antibodies and biopsied.

The mother of case 1 was negative in all antibody tests and her small intestinal mucosa was normal (villous height 521 μm, crypt depth 119 μm, intraepithelial lymphocyte count 16/100 epithelial cells). The father of case 2 was homozygous for DR3 and negative for gliadin antibodies but positive for IgA class both reticulin and endomysium antibodies (low titres 1:10). His mucosal architecture was normal (villous height 417 μm, crypt depth 112 μm, intraepithelial lymphocyte count 18/100 epithelial cells). The father of case 3 was negative for the antibody tests and normal on biopsy (villous height 506 μm, crypt depth 104 μm, slightly raised intraepithelial count 29/100 epithelial cells). The DR3 positive haploidentical son of case 4 had normal antibody titres and normal small bowel mucosal architecture (villous height 461 μm, crypt depth 126 μm, intraepithelial lymphocyte count 17/100 epithelial cells).



igure 3 Small bowel mucosal architecture of case 3 at the age of 11·4 years (upper figure) id showing tall villi irrespective of technical difficulties and at 17·5 years (lower figure). ith subtotal villous atrophy and crypt hyperplasia.



igure 4 Normal small bowel biopsy appearance of case 4 at the age of 32 years (upper ure). She had been on normal diet since early childhood. A second biopsy specimen at the e of 41 years showed clear deterioration with partial villous atrophy (lower figure).

Table 4 Case 4: clinical data and results of serum antibody studies and small bowel biopsy

	Referral	*Follow up*	
Age (years)	32·0	41·3†	41·8
Gluten in diet	Yes	Yes	No
Abdominal symptoms	Diarrhoea	None	Better
Gliadin antibodies*			
IgA	NT	0·08	<0·05
IgG	NT	62·40	4·10
Reticulin antibodies*			
IgA	NT	1:200	Negative
IgG	NT	Negative	NT
Endomysium antibodies			
IgA	NT	1:100	Negative
Biopsy	Normal	Partial villous atrophy	Normal

*Reference values: gliadin antibodies (ELISA units/ml), IgA <0·2, IgG <5·0; reticulin antibodies, negative (serum titre <1:10); and endomysium antibodies, negative (serum titre <1:5).
NT=not tested.
†Gluten free diet started after this follow up.

Table 5 HLA haplotypes of patients and their family members

Case No	*HLA*				*Family member*	*HLA*			
	A	*B*	*C*	*DR*		*A*	*B*	*C*	*DR*
1	1	8	7	3	Father	2	27	2	4
	2	27	2	4		2	22	1	4
					Mother	2	15	4	8
						1	8	7	3
					Brother	2	22	1	4
						2	15	4	8
2	2	27	2	3	Father	2	27	2	3
	3	7	—	6		3	15	3	3
					Mother	3	7	—	6
						9	27	—	4
					Brother*	2	27	2	3
						3	7	—	6
3	2	8	7	3	Father	2	8	7	3
	11	35	4	6		9	40	3	7
					Mother	11	35	4	6
						2	7	7	2
					Sister	9	40	3	7
						11	35	4	6
					Sister*	2	8	7	3
						11	35	4	6
4	2	5	7	7/9	Son*	3	7	7	2
	1	8	7	3		1	8	7	3
					Son	3	7	—	6
						1	8	7	3
					Son	3	7	7	2
						2	5	2	7/9

*Coeliac disease.

Discussion

Our four cases are identical to those previously described in the literature.[2–6] They were all first diagnosed to be free of coeliac disease and years later found to have the disease. A closer look at the initial biopsy specimens showed minor pathology in an increased count of intraepithelial lymphocyte in some cases, but still with tall villous architecture. Hence they cannot be diagnosed as having coeliac disease and treated as such. Low gluten intake may have influenced the villous architecture in two of the patients as there was one earlier diagnosed case of coeliac disease on a gluten free diet at the time of the first biopsy in the family. In fact, it has been shown that a low gluten diet has no significant effect on gross small bowel mucosal architecture in coeliac disease.[12] Another possible explanation is mucosal patchiness; flat mucosa might have been found even close to the biopsy site. We do not think this is a relevant explanation, however, because the highly sensitive and specific antibody tests used by us[9] were negative at the time of the first biopsy and later positive when mucosal atrophy was manifest.

Late developing mucosal atrophy in coeliac disease (latent coeliac disease) may be much more common than previously assumed. Recent reports indicate that coeliac disease in children is disappearing.[13 14] Our results show that coeliac disease has not disappeared; the clinical picture has changed to a milder form, resulting in an upward shift of age at diagnosis.[15] We have shown by following up birth cohorts to the age of 16 years that coeliac disease exists and appears late in the cohorts.[16] In fact, over 60% of diagnoses here are today made at school age and during adolescence. Also in adults coeliac disease often presents itself with only mild or no abdominal symptoms,[17 18] and a greater awareness of the disease has led to an increasing number of cases diagnosed annually.[19] It is hardly possible that these patients have been asymptomatic with mucosal atrophy for decades; rather one would think that the disease with mucosal atrophy has developed late. In such cases an earlier mucosal biopsy specimen would have shown normal villous architecture even if these coeliac disease patients had eaten normal amounts of gluten since early childhood.

Each of our patients had the genetic marker, HLA-DR3, which is strongly associated with coeliac disease worldwide, and also among the Finns,[20,21] and we think these patients are genetically typical coeliac disease patients. Two of the patients had HLA identical siblings suffering from the disease and one patient had a son with coeliac disease. The four first degree relatives with the same genetic marker but with normal villous architecture will be further followed up. We believe that among such cases there are those, now called possible latent cases, who will in future develop coeliac disease. One could hypothesise that for example the father of case 2 (table 5) will later develop the disease as he already has low amounts of both reticulin and endomysium antibodies detectable in his serum. On the other hand it is known that many siblings with identical HLA-DR phenotypes to their brothers or sisters with coeliac disease are healthy. It has also been shown that adding extra amounts of gluten to the diet does not produce small intestinal alterations in these healthy siblings.[22]

Taken together it can be hypothesised that factors other than genetic susceptibility and gluten ingestion are at least sometimes needed to induce mucosal damage in coeliac disease. Adenovirus, as suggested by Kagnoff *et al*,[23] could be a trigger needed in latent cases to start the immunological process in the small bowel mucosa leading to crypt hyperplastic villous atrophy typical for coeliac disease. This could also offer an explanation for the phenomenon of coeliac disease relapse over such a large range of time in patients on a normal diet containing gluten.[1,24,25]

A most important future goal is to identify latent coeliac disease and to confirm our results, that is to say, to show the development of mucosal atrophy at older ages. Early treatment of coeliac disease would thus be possible. This is important in many respects, but especially true in the light of the possible development of malignancies in patients with untreated coeliac disease.[26] One line in identifying latent coeliac disease is to measure specific autoantibodies such as IgA class reticulin and endomysium antibodies.[9] In our family study 9% of the first degree relatives of coeliac patients were found to have these antibodies together with villous atrophy.[27] Another 3% were also positive for the antibodies but had at the same time normal mucosa, and these should be followed up. Combining the antibody tests with the use of genetic markers such as DQ typing with oligonucleotides, could pick out the risk groups to be followed. Another approach would be to identify specific markers in 'normal' small intestinal mucosa. It remains to be seen whether cells expressing, for example, gamma-delta receptors are specific for coeliac disease.[28]

On the basis of the present study and the cases found in the literature it now seems that latent coeliac disease does exist. This finding will change our conceptions of this condition. Also the understanding of the heredity of coeliac disease must be re-evaluated.

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Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom

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Abstract

Ninety one patients with Kawasaki disease were examined by cross sectional echocardiography between 1980 and 1988. In the 75 patients evaluated during the acute phase of the illness (the first month), the first echocardiographic examination was carried out at a mean time of 16 days (range 5–30) and coronary arterial lesions were seen in 21 (28%). Two patients with medium sized aneurysms had myocardial infarctions, and one died. Coronary arterial lesions persisted in 17 (23%) patients, most often in younger children. The remaining 16 patients were examined from one month to four years after their acute illnesses, and this group did not have coronary arterial abnormalities. Seven patients with coronary artery lesions have reached school age and require regular echocardiographic examination and exercise electrocardiography. Selective coronary arteriography may be indicated in some patients to identify coronary artery stenosis, which the Japanese experience has shown may progress for several years after the acute illness.

It has recently become obvious that Kawasaki disease is not always self limiting or benign, as previously reported.[1] Patients without coronary artery abnormalities on echocardiography should be followed up for a long period as well as those known to have cardiac lesions. Even if patients did not have dilated coronary arterial lesions when they were acutely ill, or if they had aneurysms that had disappeared on subsequent echocardiographic examination, there is still a possibility that the disease may progress.[2] Coronary arterial intimal proliferation that developed during the acute illness could progress and cause stenotic lesions,[3 4] or juvenile arteriosclerosis.[2] These conclusions are based on work done in Japan.

The present study was carried out to establish the incidence and severity of coronary arterial abnormalities in children living in the United Kingdom, with the intention of establishing guidelines about the most appropriate method of following up patients with Kawasaki disease. We therefore reviewed the cross sectional echocardiographic findings of all patients with Kawasaki disease examined by a paediatric cardiologist between 1978 and 1988 at this hospital. The non-cardiological features of most of these patients are described in a companion paper.[5]

Patients and methods

Between 1978 and 1988 cross sectional echocardiographic examinations were carried out on 91 of 93 children in whom a diagnosis of Kawasaki disease or suspected Kawasaki disease had been made at the onset of their illness (fig 1). All became ill in the United Kingdom. All six of the diagnostic criteria of Kawasaki disease were fullfilled in 49 patients, and five criteria were met in 29 cases.[6] There were nine cases in which only four criteria were fulfilled, but four of these developed coronary arterial lesions that were seen on echocardiography during the acute illness, and in five the clinical picture was typical of the disease. The remaining six patients were referred for echocardiographic assessment after the acute illness but were said to have had clinical courses typical of the disease. There were 49 boys and 44 girls (sex ratio 1·1:1). The age of onset of the illness ranged from 3 months to 11 years. During the acute phase most of the patients (n=80, 86%) were treated with aspirin, and the remainder were given dipyridamole (n=33, 35%), gammaglobulin (n=16, 17%), steroids (n=5, 5%), or prostacyclin. Some were given antibiotics alone.

In this study the acute phase of the disease was defined as being within one month of the onset of the illness. A cardiac sequela was defined as a coronary arterial lesion which remained for more than one month after the acute onset.

The echocardiographic findings were reviewed in 91 cases; the remaining two patients had presented in 1977 and 1978 when it was not possible to assess coronary arterial anatomy by

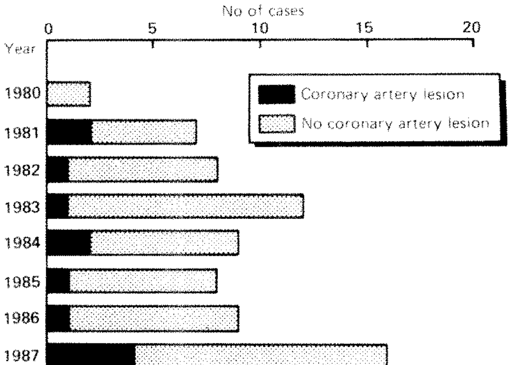

Figure 1 Number of patients examined by cross sectional echocardiography between 1980 and 1988, with and without abnormalities of the coronary arteries.

cross sectional echocardiography. Seventy five patients have been studied repeatedly since the acute phase of the illness.

The dilated lesions in the coronary arteries were classified according to the standardised diagnostic criteria of the research committee on Kawasaki disease of the Japanese Ministry of Health and Welfare.[6] A 'large' aneurysm was defined as an aneurysm the diameter of which was four times or more that of the adjacent intact coronary artery. The diameter of a 'medium' aneurysm was between one and a half and four times, and a 'small' aneurysm was less than one and a half times that of the intact coronary artery. Aneurysms change in size during the course of the disease and the measurement given is the largest diameter that was measured.

In all the examinations either a 5 MHz short focus mechanical sector scanner or a 7·5 MHz mechanical sector scanner was used.

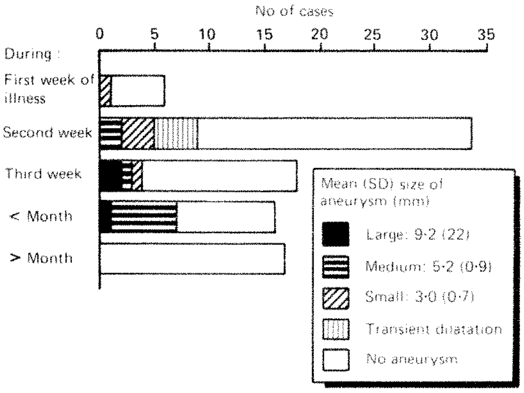

Figure 2 Time during the acute illness at which the first echocardiographic study was carried out, with the principal findings. Three, nine, and nine patients had large, medium, and small aneurysms, respectively.

FINDINGS ON CROSS SECTIONAL ECHOCARDIOGRAPHY

Seventy five children were examined by cross sectional echocardiography during the acute phase of the disease (fig 2). Sixteen children were first examined more than one month after the onset of the disease (range 32 days–4 years). Coronary artery lesions were not seen in the group of patients who presented late (fig 2).

Of the 75 patients first examined during the acute phase, cross sectional echocardiography was carried out 5–30 days after the onset of symptoms (mean (SD) 16·0 (6·5)) (fig 2). The first echocardiographic examination was made during the first week of the illness in six children, and one of these already had a small aneurysm of the left coronary artery. Thirty five children were first examined during the second week, and nine of these had coronary artery lesions. Slight dilatation was seen in four of these nine patients, and was transient (fig 3). It disappeared within the acute phase and affected only one vessel in three children, and two vessels in one child. Of the remaining five patients, small aneurysms in three children and medium sized aneurysms in two persisted for more than a month after the onset of the illness. During the third week of the disease 18 cases were examined for the first time and coronary aneurysms were detected in four children. The aneurysms were small in one, of medium size in one, and large in two (fig 4). A massive pericardial effusion was seen in one child.

The first examination was performed between three and four weeks after the onset of the illness in 16 children. Seven of the 16 cases (44%) had aneurysms on the first examination; they were of medium size in six children and large in one. Thus the incidence of coronary

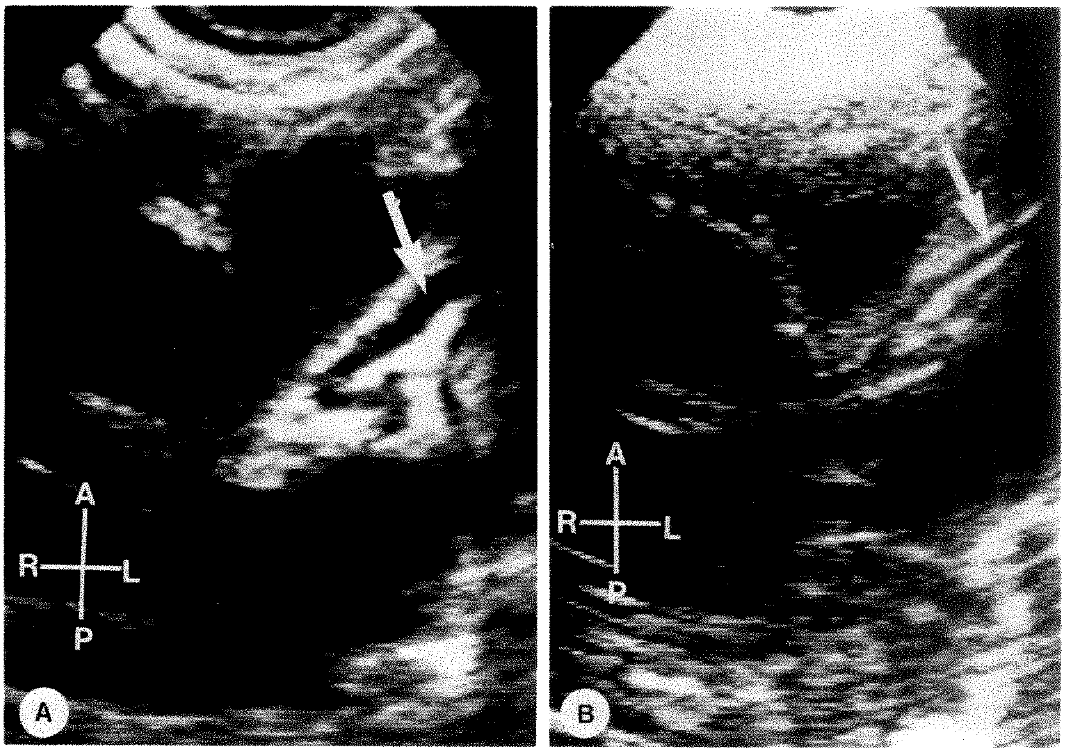

Figure 3 Patient aged 10 years. (A) Parasternal short axis view showing diffuse dilatation of left anterior descending coronary artery and circumflex branch, showing early aneurysmal formation (arrow). The aneurysm proved to be transient. (B) Normal study: parasternal short axis view showing left coronary artery. (R, right; L, left; A, anterior; P, posterior.)

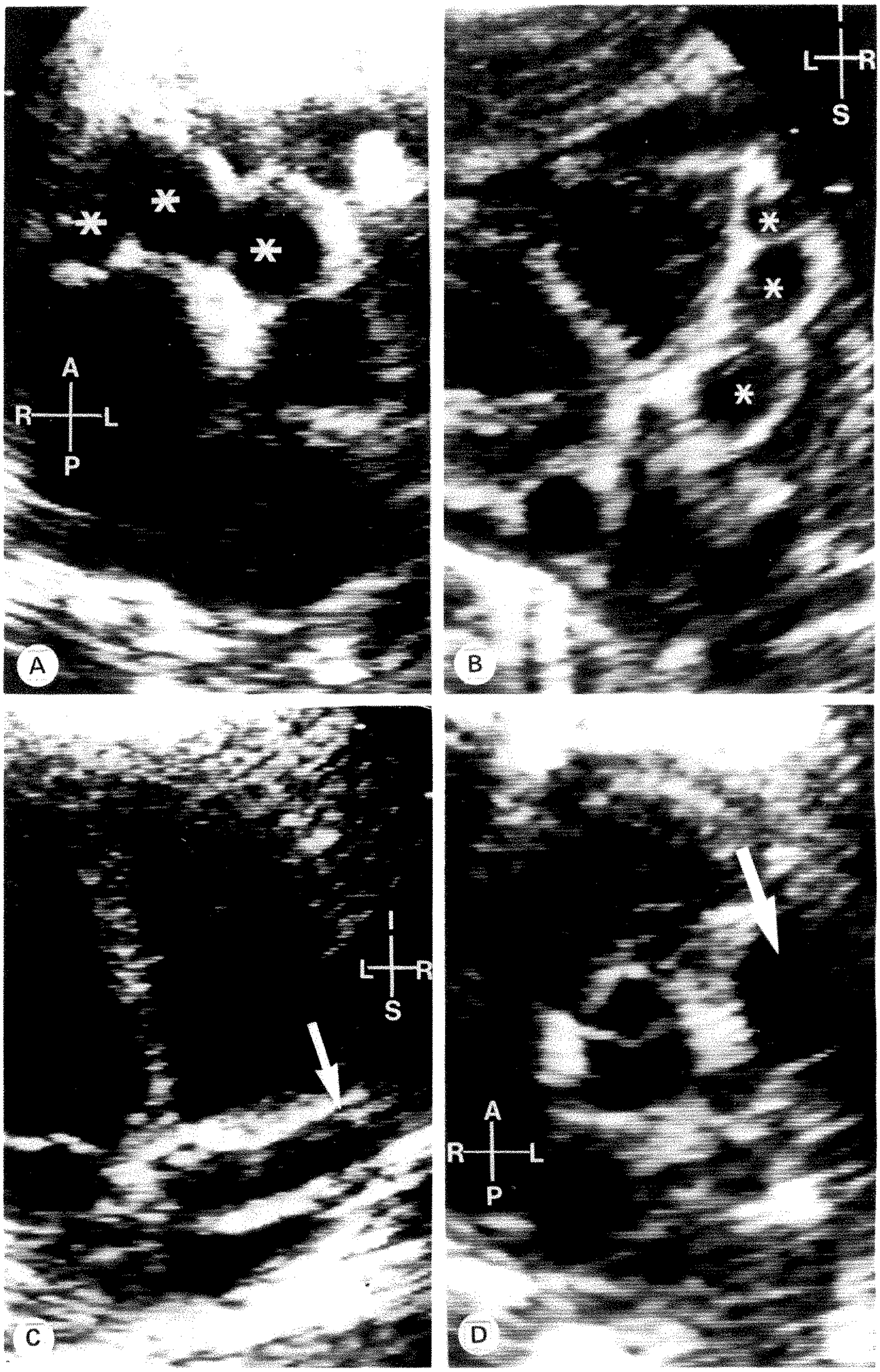

Figure 4 Patient aged 1·3 years. (A) Parasternal short axis view showing three large aneurysms in proximal right coronary artery (*). These aneurysms were still present eight months after presentation. (B) Subcostal view of aneurysms shown in (A). Note that the anatomic orientation is different from that in (A). (C) Apical four chamber view of right coronary artery showing generalised dilatation (arrow). See fig 3 (B) for control. (D) Parasternal short axis view showing large aneurysm at origin of left coronary artery (arrow). (R, right; L, left; A, anterior; P, posterior; I, inferior; S, superior.)

arterial lesions increased during the first month of the illness, being greatest during the fourth week. Three vessels were affected in nine patients, two in seven, and one in five.

In one 3 month old child cross sectional echocardiography showed medium sized aneurysms (5·0 mm) that extended into the peripheral branches of both coronary arteries and there was ventricular hypokinesis extending from the interventricular septum to the apex of the left ventricle that was associated with marked thinning of the apical myocardium (fig 5), indicat-

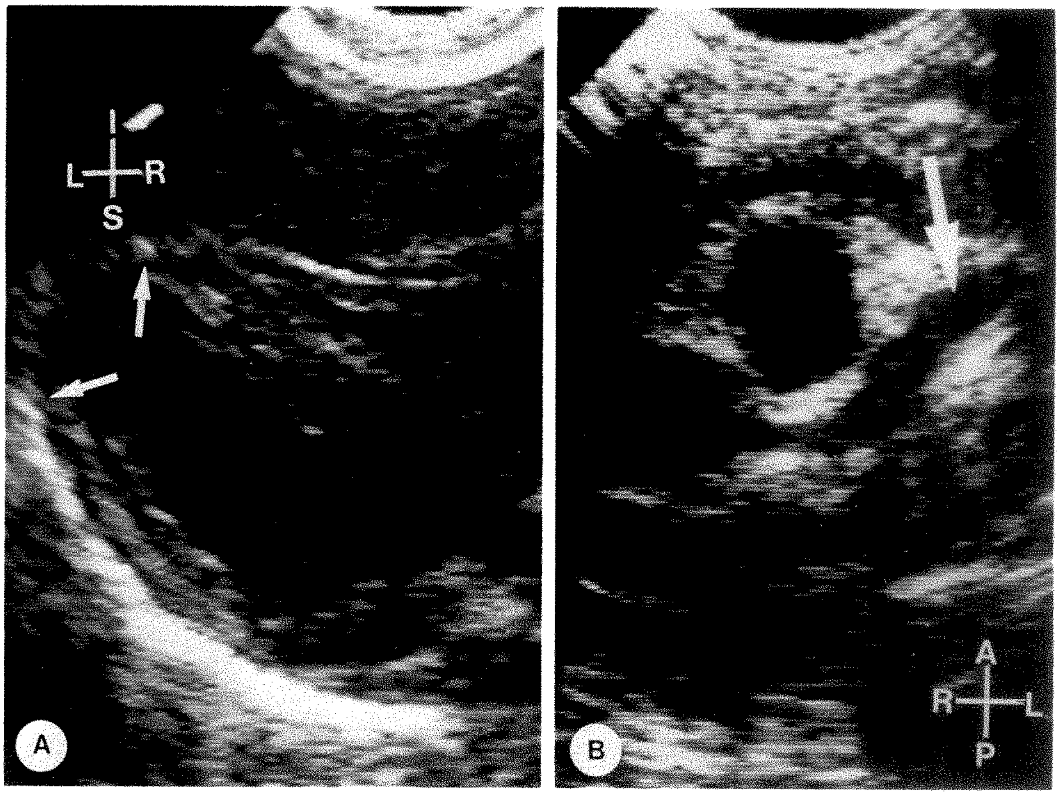

Figure 5 Patient aged 3 months. (A) Subcostal, five chamber view to show thin walled apex of left ventricle (between arrows). (B) Parasternal short axis view showing dilated left coronary artery (arrow), which has irregular margins. (R, right; L, left; A, anterior; P, posterior; I, inferior; S, superior.)

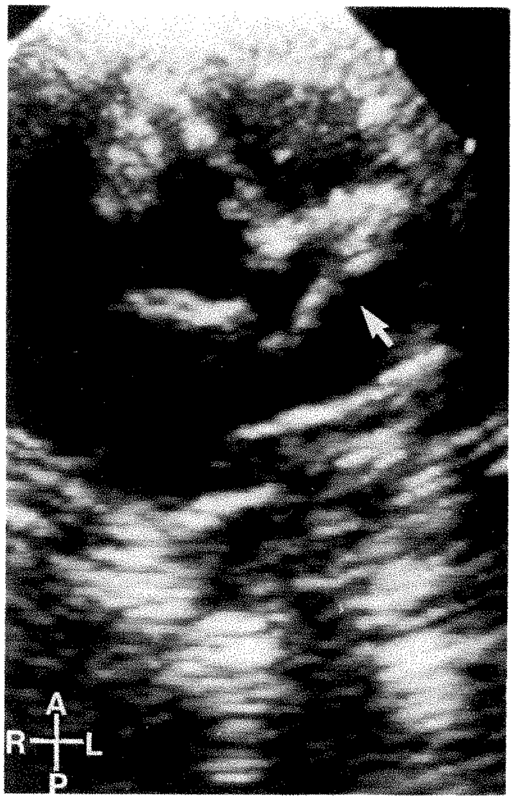

Figure 6 Patient aged 7 months. Medium sized aneurysm at bifurcation of left coronary artery (arrow), on the 24th day of the illness. She died three days later of occlusion of the left anterior descending coronary artery. (R, right; L, left; A, anterior; P, posterior.)

ing obstruction of the left anterior descending coronary artery. A patient aged 7 months had a medium sized aneurysm (3·4 mm) at the bifurcation of the left coronary artery (fig 6). She had a myocardial infarction on the 27th day of the illness from which she died, and at necropsy the left anterior descending coronary artery was found to be occluded.

Twenty one children developed coronary artery lesions during the acute phase (28%). Cardiac sequelae were seen in 17 cases, 11 of the 44 girls (25%) and six of the 49 boys (12%). A third of the children less than 1 year old developed coronary arterial sequelae, compared with four (27%) in those between the ages of 1 and 2 years, two (7%) in those between 2 and 3, and two (8%) in the older children.

Seven children in whom a coronary artery lesion was seen on echocardiographic examination during the acute phase have now reached school age. Of the 93 patients, 37 had repeat echocardiograms between six months and seven years after the acute illness. Eight children still had aneurysms 0·5 to 2·25 years later, and all were symptom free. These eight patients had had acute illnesses at a mean age of 0·8 years (range 0·3–2 years) and were re-examined at a mean age of 2·2 years (range 0·8–4·2 years). We are not aware of any late deaths.

Discussion

The number of patients with Kawasaki disease referred to this hospital for echocardiographic examination has increased gradually during the past 10 years without there being a conspicuous outbreak of the disease.[5] The referral rate increased as soon as it became apparent that coronary arterial aneurysms can be seen on cross sectional echocardiography.

Kawasaki disease was first reported in Japan in 1967,[1] and the first report of a case occurring in the United Kingdom was in 1970.[7] Comparing the cardiological pictures in Japanese and

British children,[8] the present study shows that the incidence of coronary arterial sequelae and the age at the time of the acute illness is similar. Rather more girls than boys were affected in the study group, however, than in Japan. Echocardiography was first used for the detection of coronary artery lesions in 1977.[9] Two patients in the present study presented shortly after this and they were the only patients in the series not examined by echocardiography. Echocardiographic examination during the acute phase of Kawasaki disease is desirable, as the sensitivity of echocardiography in the detection of coronary artery lesions decreases during the convalescent phase.[10, 11] This is mainly because the aneurysms shrink, and it is impossible to detect stenotic lesions with echocardiography.[10, 11] During the acute illness, coronary artery aneurysms were usually seen during the fourth week, emphasising the need to carry out serial examinations. During the acute phase only three large aneurysms were seen. According to Japanese reports,[4] only large aneurysms tend to become obstructed, but this study shows that even a moderate sized aneurysm can do so, resulting in myocardial infarction and sudden death.

In those patients who were first examined more than a month after the onset of the acute disease no coronary arterial abnormalities were seen. This does not imply, however, that they had normal coronary arteries. They could have had aneurysms that had regressed, and the coronary arteries may appear normal despite stenotic lesions.

Selective coronary arteriography has not been carried out routinely at this hospital in patients with coronary artery lesions. Echocardiographic examination has been considered to be adequate for the follow up of coronary artery lesions until patients have electrocardiographic evidence, or symptoms, of ischaemia.[8] Electrocardiographic signs of ischaemia are unreliable, however, and if present imply severe disease.[12, 13] Unfortunately, the sensitivity in detecting myocardial ischaemia on an exercise loaded electrocardiogram is also low,[13] and ventricular hypokinesis on echocardiography means there has been a myocardial infarction,[10, 11] by which time it is too late for intervention. Furthermore, children who do not have symptoms of ischaemic heart disease may die quite suddenly of infarction as a result of obstructive lesions.[11]

It seems therefore that adequate information about stenotic lesions or myocardial ischaemia may not be obtained without selective coronary arteriography[4, 12–14] or thallium myocardiography.[15] There is still debate, however, about whether the reliability of coronary angiography outweighs the benefits that accrue from it.

Some of the patients reported in this retrospective study have reached school age and are participating in physical education without being assessed for the presence of stenotic lesions in their coronary arteries. This is a cause for some concern, and in the light of Japanese experience may emphasise the need for a possible modification in the follow up protocol of affected patients. This is especially important for children who had large aneurysms in the acute phase of their disease; they may need not only echocardiography and exercise loading electrocardiography, but also thallium myocardial imaging or selective coronary arteriography, or both, before starting school. Such patients should not take part in competitive sports, and should have a cardiac evaluation every six months. Children with small aneurysms should be reviewed at least once a year. Inhibiting platelet aggregation by giving aspirin, possibly with dipyridamole, is recommended in all patients with abnormal coronary arteries. The long term management, however, has to be adapted for individual patients and determined by the state of their coronary arteries.

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Eight and 12 week courses of cyclophosphamide in nephrotic syndrome

N Ueda, K Kuno, S Ito

Abstract

Seventy three children with steroid dependent minimal change nephrotic syndrome were randomly allocated to receive treatment with cyclophosphamide (2 mg/kg/day) for either eight or 12 weeks, in combination with prednisolone. All patients had previously relapsed while the dosage was being reduced or within 14 days of discontinuing prednisolone in the six months before receiving cyclophosphamide treatment (steroid dependent), and had severe steroid toxicity. Thirty two patients were treated with cyclophosphamide for eight weeks, and 41 for 12 weeks. There were no differences between the two groups in age at onset of nephrosis or entry into the study, sex ratio, duration of nephrosis, number of relapses before entry, and follow up period after entry. The relapse free rate of patients treated for eight weeks (25%) was similar to that of those treated for 12 weeks (24%) five years after stopping the treatment, and the mean relapse free interval and the sparing effect of cyclophosphamide (if any) on subsequent treatment with steroids did not differ between the groups. We conclude that cyclophosphamide should be used for no longer than eight weeks at a dose of 2 mg/kg/day in children with steroid dependent minimal change nephrotic syndrome.

Cyclophosphamide has been widely used in combination with corticosteroids (steroids) to treat children with frequently relapsing nephrotic syndrome and produces a long remission.[1–10] The side effects of cyclophosphamide such as bone marrow suppression,[2 11] gonadal toxicity,[12] and possibly oncogenicity[4] seem to be dose related. If the drug is to be used in frequently relapsing nephrotic patients, we must, therefore, use the lowest effective dosage, keeping the risk of long range toxicity as low as possible. Previous studies suggested that children with frequently relapsing nephrotic syndrome without steroid dependence could be more successfully treated with cyclophosphamide than those with steroid dependence.[8 9] Other authors have compared eight week and 12 week courses of cyclophosphamide, and reported that a 12 week course of treatment is more likely to result in sustained remission in steroid dependent nephrotic patients.[10] Despite the results of this relatively small study, it is still uncertain whether cyclophosphamide is more effective when given for 12 weeks than for eight weeks to treat steroid dependent nephrotic patients with minimal change.

The present prospective study was designed to determine whether eight week or 12 week courses of cyclophosphamide at a dose of 2 mg/kg/day were more effective in a large number of children with steroid dependent minimal change nephrotic syndrome who had severe steroid toxicity.

Patients and methods

From February 1975 to August 1988, 73 children (54 boys) with steroid dependent minimal change nephrotic syndrome confirmed by the classic clinical and laboratory features and histological examination of a renal biopsy specimen were treated with a combination of prednisolone and cyclophosphamide.[3] All patients had relapsed while the dose of prednisolone was being reduced, or within 14 days of discontinuing prednisolone, in the six months before cyclophosphamide treatment (steroid dependent). They developed at least two of the following features of steroid toxicity due to the long term steroid treatment: arrest of growth, hypertension, gross cushingoid appearance, osteoporosis, psychosis, diabetes, cataracts, and glaucoma.

Because of steroid dependence and severe steroid toxicity, each patient was randomly allocated to one of the following two treatment regimens of cyclophosphamide after remission had been induced: 2 mg/kg/day of cyclophosphamide for eight weeks (total dosage, 112 mg/kg), or the same daily dose for 12 weeks (total dosage, 168 mg/kg). None of the patients had received any relevant drugs other than prednisolone before the course of cyclophosphamide. Informed consent was obtained from the parents of each patient.

The initial episode of the nephrotic syndrome and all relapses during the period of observation (proteinuria $\geqslant 40$ mg/hour/m^2 for three consecutive days) were treated with prednisolone in divided doses of 60 mg/m^2 per day for four weeks, with the dose being tapered by 5 to 10 mg/m^2 every two weeks during the next three to four months. Those patients who had milder degrees of proteinuria (greater than 4 mg/hour/m^2 but less than 40 mg/hour/m^2) were managed with the previous maintenance dose of prednisolone for one to two weeks, the dose either being increased to 60 mg/m^2/day if remission (<4 mg/hour/m^2 for three consecutive days) was not achieved, or decreased after at least one week of remission of proteinuria.

During the course of cyclophosphamide the white cell count was estimated weekly, and the drug was discontinued if the total count was

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below 4·0×10⁹/l. Cyclophosphamide was reinstituted at the previous dosage level after the white blood cell count had increased to 4·0×10⁹/l or more.

To assess the effect of the two regimens of cyclophosphamide the following variables were compared: the relapse free rate and relapse free interval after cyclophosphamide treatment, the mean number of relapses, the mean cumulative dosage of prednisolone, and the mean total time not taking prednisolone before and after the course of cyclophosphamide. Acute side effects such as leucopenia, thrombocytopenia, haemorrhagic cystitis, alopecia, and infections, were recorded.

Results were expressed as mean (SD). χ^2 analysis was used to analyse the differences between groups is sex ratio, relapse free rate after cyclophosphamide treatment, and incidence of toxic reactions to the drug. The two tailed Student's *t* test was used to analyse the means of other variables, and the cumulative percentage of remission after cyclophosphamide treatment was plotted by the time to relapse curve, as previously described.[6 13]

Results

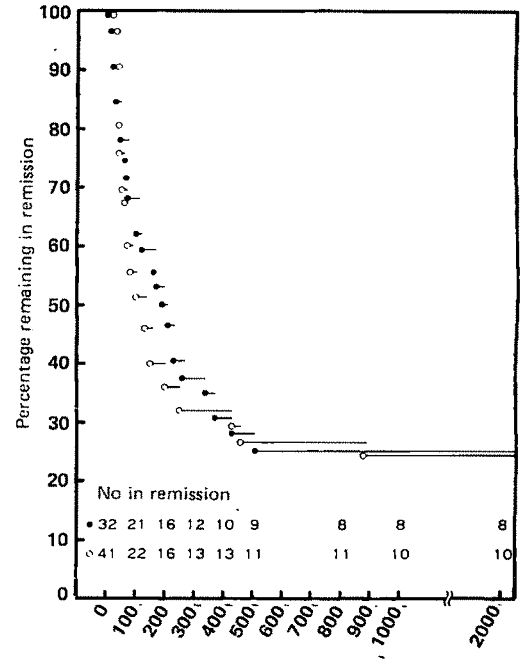
Seventy three patients entered into the study; 32 patients were treated with cyclophosphamide for eight weeks, and the remaining 41 were treated for 12 weeks. The mean ages at onset of nephrosis and at entry into the study, sex ratio, the mean duration of nephrosis before entry, and the mean period of follow up after cyclophosphamide treatment were similar in the two groups (table 1). There were no significant differences between the two groups in the mean number of relapses or the mean cumulative dosage of prednisolone before entry.

Only eight of the 32 patients (25%) treated with cyclophosphamide for eight weeks, and 10 of the 41 patients (24%) treated for 12 weeks were still in remission at the end of the period of observation (table 2). In patients who had not relapsed the mean interval was 76·5 (38·6) and 71·3 (23·3) months in those treated for eight weeks and 12 weeks respectively, and the difference was not significant. In patients who relapsed after cyclophosphamide treatment, the mean interval without relapse was 4·9 (4·6) and 4·0 (5·4) months for those treated for eight weeks and 12 weeks, respectively. All but one of the relapses after cyclophosphamide occurred within two years of discontinuing treatment—the longest was a patient treated for 12 weeks who relapsed at 29 months. No significant differences were noted between the groups of relapsed patients in the mean number of relapses, the mean cumulative dosage of prednisolone, or the mean total time not taking prednisolone after the course of cyclophosphamide.

Table 1 Details of patients studied. Values are expressed as mean (SD) except where otherwise stated

	Cyclophosphamide for eight weeks (n=32)	*Cyclophosphamide for 12 weeks (n=41)*
Male:female ratio	26:6	28:13
Age at onset of nephrosis (years)	6·0 (3·4)	6·4 (3·7)
Age at entry into the study (years)	7·7 (3·7)	7·8 (3·7)
Duration of nephrosis before entry (months)	18·8 (20·9)	19·2 (25·3)
Length of follow up after entry (months)	66·2 (50·6)	63·1 (33·7)
No of relapses before entry (/patient/year)	4·5 (1·8)	5·1 (2·3)
Cumulative dosage of prednisolone before entry (mg/kg/month follow up)	19·3 (9·6)	18·5 (8·0)

The figure shows the 'time to relapse' curves of patients treated with eight week and 12 week courses of cyclophosphamide.[6 13] There was no significant difference in the cumulative percentage of remission at the end of five years after discontinuing cyclophosphamide.



Time to relapse curves[6 13] of children with steroid dependent minimal change nephrotic syndrome after eight week (●) and 12 week (○) courses of cyclophosphamide.

Table 2 Clinical data of patients after treatment with cyclophosphamide. Values are expressed as mean (SD)

	Cyclophosphamide for eight weeks		*Cyclophosphamide for 12 weeks*	
	No relapse (n=8)	*Relapse (n=24)*	*No replase (n=10)*	*Relapse (n=31)*
Interval without relapse after entry (months)	76·5 (38·6)	4·9 (4·6)	71·3 (23·3)	4·0 (5·4)
No of relapses (/patient/year):				
Before entry	4·4 (2·6)	4·5 (1·5)	4·5 (2·0)	5·3 (2·3)
After entry	0	2·9 (1·6)	0	3·5 (3·8)
Cumulative dosage of prednisolone (mg/kg/month follow up):				
Before entry	16·0 (8·2)	20·5 (9·9)	16·9 (6·5)	19·1 (8·5)
After entry	1·2 (0·3)	11·1 (8·2)	0·8 (0·5)	12·1 (8·5)
Total time not taking prednisolone (months):				
Before entry	2·4 (4·5)	2·0 (2·9)	1·2 (2·8)	3·2 (5·6)
After entry	69·9 (44·0)	33·9 (51·3)	68·6 (21·3)	25·8 (34·7)

As there was no difference in outcome between the groups, the clinical features were compared between patients who relapsed ($n=55$) and those who did not ($n=18$). There were no significant differences between these groups in sex ratio, age at onset of nephrosis, duration of nephrosis, and the number of relapses before cyclophosphamide treatment. Patients who did not relapse, however, were significantly older when they entered the study (9·3 (4·3) years) than those who did (7·3 (3·3) years), ($p<0\cdot05$).

Nine of the 32 patients treated for eight weeks became leucopenic compared with 14 of the 41 patients treated for 12 weeks. A short interruption of the treatment was necessary in only eight patients, and bone marrow suppression was reversible. There were no other side effects such as thrombocytopenia, haemorrhagic cystitis, alopecia, or infections.

Discussion

Prolongation of cyclophosphamide treatment has been shown to induce a higher rate of long lasting remission; treatment for six weeks or less seemed to be less effective,[1 7] and a higher cumulative dosage of cyclophosphamide than that used in our study has been reported to produce a long remission.[2–7 10] Because the complications of cyclophosphamide such as bone marrow suppression,[2 11] gonadal toxicity,[12] or oncogenicity[4] are likely to be dose related, the two treatment protocols were compared for the treatment of children with steroid dependent nephrotic syndrome. In the present prospective study, the two treatment groups were comparable for clinical features, the mean duration of nephrosis, the mean number of relapses, and the mean cumulative dosage of prednisolone before entry, and the mean period of follow up after cyclophosphamide treatment. We found that the effect of an eight week course of cyclophosphamide on remission rate and its sparing effect on subsequent steroid therapy, if any, were the same as that of the 12 week course in children with steroid dependent minimal change nephrotic syndrome.

Several studies have reported separate evaluation of the effect of cyclophosphamide between non-steroid dependent and steroid dependent patients with minimal change nephrotic syndrome.[8–10] In view of this, our data are comparable with these reports (table 3). Both Garin *et al*[8] and Arbeitsgemeinschaft fur Padiatrische Nephrologie[9] found that non-steroid dependent nephrotic patients responded favourably, with prolonged remissions, to treatment for eight weeks or longer, whereas steroid dependent patients did not have such benefits. Nevertheless, a recent report of the same German group has shown that in steroid dependent patients with minimal change nephrotic syndrome, a 12 week course of cyclophosphamide at a dose of 2 mg/kg/day was associated with a significantly higher two year relapse free rate (67%) than that after only an eight week course (22%) (table 3).[10] In contrast, the relapse free rate of our patients treated for eight weeks (25%) was the same as that of those treated for 12 weeks (24%) five years after the end of the treatment; these figures were comparable with those of steroid dependent patients treated for eight weeks in the two other reports.[8 10] Of the 13 steroid dependent patients in the study of Garin *et al*,[8] the three patients who did not relapse after cyclophosphamide were treated for either eight or nine weeks, but half of the other 10 patients who relapsed after the treatment were treated for 12 weeks or longer. These data support our contention that the use of cyclophosphamide for longer than eight weeks has no benefit in steroid dependent patients with minimal change nephrotic syndrome.

The reason for the difference in the effect of cyclophosphamide in steroid dependent patients with minimal change nephrotic syndrome between our results and those in the second German report is unclear.[10] Their criteria for steroid dependence, the age at onset of nephrosis, and the number of relapses before cyclophosphamide treatment were similar to ours. The mean age at entry into the study of their patients treated for 12 weeks who had higher relapse free rate (approximately 9 years) was, however, similar to that of our total

able 3 Cyclophosphamide in steroid dependent and frequently relapsing nephrotic syndrome

tudy	*Steroid dependent*					*Frequently relapsing*				
	Age at onset of nephrotic syndrome (months)	*Duration of nephrotic syndrome before trial (months)*	*No of relapses*	*Cumulative % of sustained remission*	*Follow up after treatment (months)*	*Age at onset of nephrotic syndrome (months)*	*Duration of nephrotic syndrome before trial (months)*	*No of relapses*	*Cumulative % of sustained remission*	*Follow up after treatment (months)*
arin *et al* (retrospective)[8]:										
Cyclophosphamide 2 mg/kg for 6–40 weeks	36	45	10/13	23	32	29	45	3/10	70	20
rbeitsgemeinschaft fur Padiatrische Nephrologie (prospective)[9]:										
Cyclophosphamide 2 mg/kg for eight weeks	60	22	22/34	28	30	64	39	4/16	72	30
or										
Chlorambucil 0·15 mg/kg for eight weeks	49	37				63	41			
rbeitsgemeinschaft fur Padiatrische Nephrologie[10]:										
Cyclophosphamide 2 mg/kg for 12 weeks (prospective)	69	34	6/18	67	24					
Cyclophosphamide 2 mg/kg for eight weeks (retrospective)	58	22	14/18	22	24					
resent study (prospective):										
Cyclophosphamide 2 mg/kg for 12 weeks	76	19	31/41	24	60					
Cyclophosphamide 2 mg/kg for eight weeks	72	19	24/32	25	60					

patients who did not relapse (9·3 years), but was higher than that of their patients treated for eight weeks (6·9 years) and of our total patients who did relapse (7·3 years). Furthermore, all their patients who relapsed after cyclophosphamide did so within 400 days of the end of the course, but five of our patients relapsed later. Therefore the difference in age at the time that treatment was instituted or the period of follow up after treatment, or both, might account for the conflicting results—namely, the low cumulative percentage of sustained remission. The main factor determining the effect of cytotoxic treatment in steroid dependent patients with minimal change nephrotic syndrome seems to be primary resistance of the individual patient to the cytotoxic drugs, which may partly be related to the age at the time that treatment is instituted, as suggested by our study and that of Barratt *et al.*[6] In an era when an increasing number of immunosuppressive agents are being used for the treatment of steroid responsive or steroid dependent nephrotic syndromes, it should be emphasised that two to three year periods of follow up are necessary to assess the effect of a trial of such a drug.

The ultimate prognosis for children with frequently relapsing nephrotic syndrome is usually good,[14 15] and exposure to the potentially serious toxic effects of cytotoxic drugs must be viewed with concern and kept as short as possible. Although we found no difference in the incidence of toxic reactions to cyclophosphamide between the two treatment protocols, there are insufficient data to determine the relationship between the dose and the duration of cyclophosphamide treatment and the degree of severity of long standing side effects on the reproductive system and the development of neoplasia. Therefore if cyclophosphamide has to be given to steroid dependent nephrotic patients because of unacceptable steroid toxicity or difficulty in controlling the disease, it should be used for no longer than eight weeks at a dose of 2 mg/kg/day to reduce the risk of development of late toxic effects as far as possible.

In summary, the effect of an eight week course of cyclophosphamide seems to be the same as that of a course of 12 weeks in children with steroid dependent minimal change nephrotic syndrome. We conclude that cyclophosphamide should be used for no longer than eight weeks for the treatment of these patients. Nevertheless, it should be noted that the proportion of children with steroid dependent minimal change nephrotic syndrome who are likely to benefit from cytotoxic treatment is quite small.

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Continuous papaveretum infusion for the control of pain in painful sickling crisis

Patricia C E Sartori, Graham J Gordon, Philip J Darbyshire

Abstract

We describe our experience of using continuous papaveretum infusions to control pain in 24 children admitted on 45 occasions with painful sickling crisis. The children were aged from 1·7 to 14·3 years. Infusion duration ranged from one to nine days (median three days), total dose from 0·3 to 21 mg/kg (median 2·4 mg/kg), with a pronounced tendency for dosage to increase with increasing age. No respiratory depression was observed. One infusion was discontinued because of cerebral toxicity.

It is well recognised that analgesia for children is frequently underprescribed and underadministered.[1 2] For children intramuscular injections can themselves be a source of pain and apprehension.[2] The use of opiate infusions for children with postoperative or terminal pain is now well established.[3–5] Children with sickle disease may suffer repeated episodes of severe pain during sickling crises. The standard treatment for these is hydration and analgesia.[6] Analgesia is often delivered in the form of intermittent intramuscular opiates, although there is increasing use of opiate infusions.[6–8] In 1988 we introduced continuous papaveretum infusions as the preferred method of providing analgesia for severe sickling crisis.

Patients and methods

Over 18 months, 24 children aged 1·7 to 14·3 years presented with severe sickling crisis on 45 occasions. Eighteen had homozygous sickle cell disease, four had sickle cell haemoglobin C disease, and two sickle/β° thalassaemia. On 19 occasions the site of pain was in the limbs, on 11 occasions in the back or abdomen, and on 15 in multiple sites. None of these children fulfilled the exclusion criteria listed below and all received a papaveretum infusion.

PROTOCOL

A papaveretum infusion was administered to any child with a sickling crisis sufficiently painful to warrant opiate analgesia, excluding any with the following disorders: (i) pre-existing respiratory depression secondary to pulmonary or neurological problems or (ii) active cholecystitis and biliary colic.

The infusion was made up as papaveretum 1 mg/kg in 60 ml of dextrose saline solution and delivered via a syringe driver. A 3 ml bolus (50 μg/kg) was given initially and the rate set at 3 ml/hour for the first hour. Nursing staff assessed the level of pain hourly and adjusted the infusion rate to keep the child pain free or comfortable, usually between 2 ml/hour and 6 ml/hour (33–100 μg/kg/hour). Higher rates were used occasionally after discussion with medical staff. When pain was abolished the rate was gradually reduced, and an oral analgesic such as paracetamol was administered before the infusion was discontinued.

Respiratory rate was recorded hourly and conscious level was monitored informally.

In a subgroup of 11 children aged 4·5 to 12·2 years the effectiveness of analgesia was evaluated using a five point pain analogue scale (see fig 1).[9] The scale was explained to the child and then he/she was asked to grade the severity of the pain hourly while awake. This score was used by nursing staff in their evaluation of pain.

Results

There was wide variation in the duration of the infusions (see table 1). During most painful episodes (n=30) infusions were given for one to three days, but a small number (n=6) required continuing intravenous analgesia for five to nine days. Variation in dosage was also wide with more than half of the infusions peaking at a daily dose in excess of the standard recommended dose (0·9 mg/kg daily, derived from 150 μg/kg every four to six hours). Although no individual patterns could be discerned, there was a pronounced trend for older children to receive higher doses (per kg) and infusions of longer duration (see fig 2). This correlation reached significance for both maximum hourly rate and maximum daily dose.

There was some variation in dosage between children with different haematological diagnoses, children with sickle/β° thalassaemia requiring higher doses than children with homozygous sickle cell disease or sickle cell haemoglobin C disease, but these observations are based on small numbers.

The results of the subgroup of 11 children evaluated by the pain analogue scale are shown in table 2. The dosage and duration of infusion in this group did not differ from the group as a whole. Pain scores varied widely with 50% of children pain free for at least 44% of the hours studied, and with moderate to severe pain for less than 12% of the time. In contrast other children had moderate to severe pain for up to 37% of the hours studied and were pain free for as little as 17% of the time.

No respiratory toxicity was observed. Most of the patients were tachypnoeic on admission,

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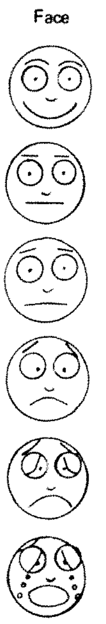

Severity of pain	Numerical score
No pain (no hurt)	0
Very mild pain (a little hurt)	1
Mild pain (a bit more hurt)	2
Moderate pain (a big hurt)	3
Severe pain (a very big hurt)	4
Very severe pain (the worst hurt you can imagine)	5

For each child, the nurse ascertained his/her vocabulary for pain and using the appropriate words (examples in brackets) described the faces to the child and asked him/her to choose the one which best expressed the child's degree of pain.

Figure 1 Description of the 'faces' pain scale used with younger children.

Table 1 The duration and dosage of papaveretum infusions in 45 episodes of painful sickling crisis. Results given as range (median)

Age (years)	No of episodes	Duration of infusion (days)	Maximum rate* (μg/kg/hour)	Maximum dose† (mg/kg/day)	Total dose‡ (mg/kg)
0–5	18	1–6 (2)	30–130 (60)	0·3–2·1 (0·9)	0·3–7·2 (1·5)
5–10	17	1–9 (3)	40–140 (68)	0·5–3·4 (1·3)	0·7–10·9 (2·4)
10–15	10	2–8 (3)	48–180 (100)	0·5–4·3 (1·5)	0·8–21·1 (2·9)
Total	45	1–9 (3)	30–180 (70)	0·3–4·3 (1·3)	0·3–21 (2·4)
Correlation§		+0·26	+0·43	+0·44	+0·32
p Value		<0·1	<0·005	<0·005	<0·05

*Maximum rate: highest hourly rate/kg of each papaveretum infusion.
†Maximum dose: highest daily dose/kg of papaveretum given during each infusion.
‡Total dose: total dose/kg of papaveretum given during a single admission.
§Correlation: correlation coefficient of age plotted against dose and duration.

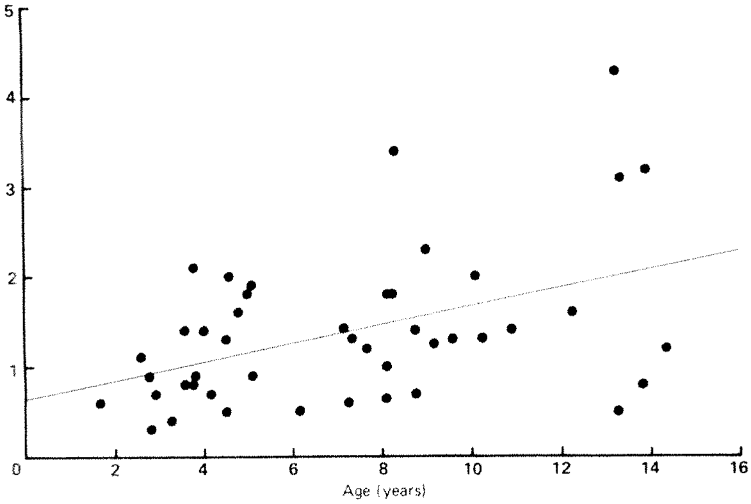

Figure 2 The highest daily dose/kg of papaveretum given during each infusion plotted against the patients' age. Correlation coefficient +0·44, p<0·005.

Table 2 Age of patients, dose of papaveretum, and pain chart scores for episodes monitored by pain charts

		Range (median)	
Age (years)		4·5–12·2 (7·3)	
Maximum dose/day (mg/kg/day)		0·5–3·4 (1·6)	
Total dose (mg/kg)		0·5–10·9 (3·3)	
Duration (days)		1–9 (4)	
No of hours chart used		18–126 (48)	
Score	0	1–2	3–5
Range (median) % of time when pain score was as shown*	17–83 (44)	16–80 (39)	0–37 (12)

*Number of hours when pain score='n'÷ number of hours pain charts used×100.

with a subsequent fall in respiratory rate. Neurological toxicity was seen on one occasion in a 10 year old boy. The infusion was discontinued because of appreciable drowsiness and an alteration in conscious level, which resolved over 12 hours after stopping the infusion. This occurred when he was receiving a dose of 1·3 mg/kg/day. He had previously received 2 mg/kg/day and 2·3 mg/kg/day without ill effect.

Discussion

It is recognised that prescription and administration of analgesics for children is often inadequate when compared with adults.[1] Continuous opiate infusion provides a strategy for ensuring the delivery of analgesic medication to children without relying on painful intramuscular injections.[2] Experience with continuous opiate infusions is most extensive in the postoperative setting, where its safety is well established. Dilworth and MacKeller describe more than 600 consecutive opiate infusions in children with only seven episodes of respiratory depression, all resolving with reduction of the infusion rate without naloxone.[5] Minor toxicity, such as nausea and vomiting, occurred in 25%, a similar proportion to that experienced with other postoperative analgesic regimes.

The efficacy of analgesia is most frequently assessed by using a linear analogue scale to describe the degree of pain. Pain score data from comparative studies in adults and children show a consistent improvement in the quality of analgesia delivered by continuous opiate infusion compared with 'as required' or regular intramuscular injections of the same drugs.[4 10 11] Several studies have shown that higher doses of analgesic are delivered to patients on continuous infusions compared with those receiving intermittent medication.[4 11] Taken together with data on analgesic administration patterns in children,[1] this suggests that part of the mechanism for better analgesia may be that continuous infusion overcomes the habitual underadministration of analgesia for children. That this is not the entire explanation may be inferred from a comparative study in adults in which the total dose of analgesia was significantly lower in the continuous infusion group by a factor of two to three, but this group also had significantly lower scores on a pain analogue scale.[10]

The use of continuous opiate infusions in children with terminal malignancy is an accepted method of providing analgesia. In the study of Miser *et al* there was considerable variation in dosage, with most patients experiencing adequate analgesia with standard doses of morphine, but two patients required considerably higher doses.[3]

Experience with continuous opiate infusions in painful sickling crisis is increasing.[6–8] In the series of Cole *et al* there was a fivefold variation in maximal dose with a mean of 2·4 mg/kg/day of morphine.[7]

In our series the most striking feature was the extremely wide interindividual and intraindividual variation in dosage, both during and between episodes. In most patients pain was well controlled with doses of 1·3 mg/kg/day (median) but a small number needed substantially higher doses. We observed a consistent increase of dosage per kg with age. This was felt to reflect the increasing severity of painful sickling crises with age, although a better ability to express pain may have played a part.

Pain charts were used prospectively in a selected group to adjust the rate of infusion. The scores obtained can also be used as a measure of the efficacy of analgesia, and they confirm the impression that adequate analgesia was easily achieved in the majority, but required increasing analgesia for several days in a minority. There was no difference in the amount of papaveretum given to children using and not using pain charts but numbers were small and selection was not random so the effects of using pain charts on dosage cannot be fully assessed.

Toxicity is a major limiting factor with opiates given by any route particularly if high doses are used. We observed no respiratory depression but one episode of neurological toxicity necessitated interruption of the infusion. This episode was not dose related and was thought to represent an idiosyncratic reaction. It serves to underline the importance of monitoring the conscious level in all children on opiate infusions at whatever dose.

In summary, sickling crises vary in severity and duration requiring a flexible approach in providing analgesia. Continuous intravenous infusion of papaveretum provides a flexible means of delivering continuous analgesia which is acceptable to patients and relatively simple to administer. It should therefore be considered as the preferred method of providing analgesia in severe sickling crisis.

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Red cell membrane sodium transport: possible genetic role and use in identifying patients at risk of essential hypertension

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Abstract
To investigate the influence of a family history of essential hypertension on abnormalities of red cell membrane sodium transport, 28 hypertensive children and their families were studied. In 15 families one or both parents had either essential hypertension or a strong family history. In 13 families neither parent had essential hypertension or a positive family history. There were significant differences between the children with a positive family history of essential hypertension compared with those without. Values are expressed as mean (SD): intracellular sodium concentration (mmol/l cells) 8·19 (2·18) compared with 6·41 (0·98); sodium efflux rate constant 0·4873 (0·1379) compared with 0·5831 (0·1104); and numbers of sodium-potassium ATPase pump sites (BMax) (nmol/l cells) 7·96 (1·71) compared with 9·56 (1·7). Significant differences were also found when the index hypertensive children were excluded and the normotensive siblings with and without hypertensive family histories were compared. These data suggest that abnormal red cell membrane sodium transport has a familial component, and although it is not caused by the hypertension it may be the earliest pathophysiological step in its development, perhaps allowing the identification of children at risk of essential hypertension.

Essential (primary) hypertension is an important cause of morbidity and mortality among adults, and probably has its origins in childhood. As yet, however, we do not have a means of identifying children at risk of developing it. Despite extensive research the aetiology of essential hypertension is still unclear, although many different mechanisms have been suggested. An understanding of the pathophysiological mechanisms of the development of essential hypertension, and the detection of those children who are at risk, may give us the opportunity to alter the natural history of the disease.

During recent years it has increasingly been realised that a disturbance of the transmembrane distribution of ions is a feature of hypertension in man. In particular, abnormalities of sodium transport across cell membranes have been extensively reported. Since Losse *et al* in 1960 first described raised intracellular sodium concentration in the red blood cells of adults with essential hypertension,[1] abnormalities in other cells not directly concerned in pressure regulation (such as polymorphonuclear leucocytes and lymphocytes) have been reported,[2 3] as have abnormalities in cells that are more directly concerned such as the smooth muscle cells of resistance vessels.[4] Sodium transport across red blood cell membranes occurs primarily by four mechanisms to maintain the intracellular sodium concentration: the sodium-potassium ATPase dependent pump, sodium-potassium cotransport, sodium-sodium (measured as sodium-lithium) countertransport, and passive sodium diffusion. Passive diffusion of sodium occurs across the membrane along a concentration gradient. Abnormalities of the three other pathways have all been reported in essential hypertension.

Activity of the sodium-lithium countertransport pathway is increased in essential hypertension,[5] but because in man this pathway exchanges a single external sodium ion for a single internal sodium ion—and therefore will not result in any net change in intracellular sodium concentration—it seems unlikely that the pathway is of pathophysiological importance.

Activity of the sodium-potassium cotransport pathway is decreased in patients with essential hypertension.[6] The pathway normally lies dormant in the cell membrane, however, unless intracellular sodium concentration rises above a critical point at which time the sodium pump is being maximally stimulated and the sodium-potassium cotransport system is acting as a supporting mechanism for sodium extrusion. It is therefore unlikely that this pathway has any pathophysiological importance.

The sodium-potassium ATPase pump has been widely studied in essential hypertension, and we have chosen to study this pathway by measurement of the intracellular sodium concentration, the sodium efflux rate constant, and the number of sodium-potassium ATPase dependent pump sites. We have previously described abnormalities of these three measures of sodium transport in children with essential hypertension compared with normal children, and with children with secondary forms of hypertension.[7] The children with essential hypertension had raised intracellular sodium concentrations, lowered sodium efflux rate constants, and decreased numbers of sodium-potassium ATPase dependent pump sites compared with the normal children and those with secondary hypertension. There was, however, some degree of overlap of values among these three groups. It is unclear whether these abnormalities are important in the development of essential hypertension, or whether they are genetic markers. To study these

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abnormalities further and investigate the influence of a family history of hypertension we have therefore studied families with and without a history of hypertension.

Subjects and methods

We studied 28 families consisting of the parents and siblings of 28 children who presented for the investigation of mild to moderate hypertension. Of these index 28 children, 15 were subsequently found to have secondary forms of hypertension and 13 had essential or labile hypertension.

The 28 families were divided into two groups. Families in which one or other of the parents had essential hypertension, or had a strong positive hypertensive family history, were defined as our 'positive family history' group; 15 families fulfilled these criteria. In 13 families neither parent was hypertensive nor had a hypertensive family history, and these families were allocated to our 'negative family history' group. We studied 58 children including the index 28 hypertensive children, 30 in the positive family history group, and 28 in the negative family history group (table 1).

Blood pressure was measured in all subjects using a randon zero sphygmomanometer. The mean of three separate recordings for each subject was obtained and expressed as SD scores using the recommendations of the first American Task Force on blood pressure control in children.[8] Blood was taken for red cell sodium transport studies, and urea, electrolytes, and creatinine estimation. A random urine specimen was obtained for analysis of sodium and creatinine concentrations and from these urine sodium excretion was estimated.[9]

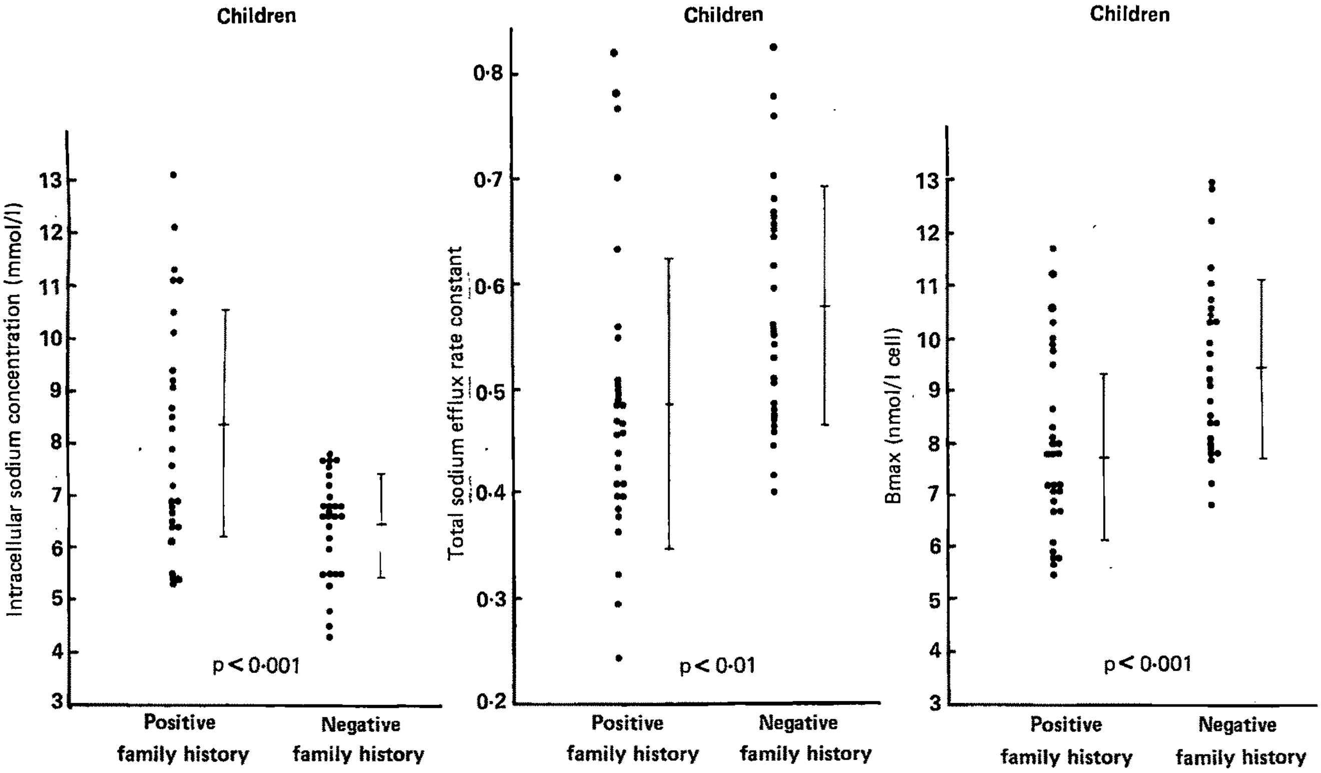
Intracellular sodium concentration was measured on washed red blood cells using a flame photometer and expressed as mmol/l cells. Sodium efflux rate constant was measured after the incubation of red blood cells with ^{22}Na and the number of sodium-potassium ATPase dependent pump sites was estimated by measuring the binding of labelled ouabain to the red cell membrane (BMax) by the methods descri-

Table 1 Details of the index children and their siblings studied. There were no significant differences between the groups.

	No with positive family history (n=30)	*No with negative family history (n=28)*
Male:female ratio	19:11	14:14
Mean (range) age (years)	13·79 (0·25–22·3)	14·22 (5·8–33)
Mean (range) systolic blood pressure (mm Hg)	121·4 (80–166)	121·8 (84–180)
Mean (SD) systolic blood pressure SD score	0·92 (1·38)	1·16 (1·86)
Mean (range) diastolic blood pressure (mm Hg)	73·2 (50–94)	76·1 (32–140)
Mean (SD) diastolic blood pressure SD score	0·80 (1·09)	0·99 (2·07)
Mean (SD) sodium excretion (mmol/kg/24 hours)	1·62 (0·75)	1·83 (1·27)

Table 2 Results of red cell membrane sodium transport in parents

	Hypertensive patients (n=18)	*Normotensive parents (n=36)*	*p Value*
Mean (SD) intracellular sodium concentration (mmol/l cells)	9·05 (3·6)	6·29 (1·45)	<0·001
Mean (SD) sodium efflux rate constant	0·4470 (0·1052)	0·6091 (0·1500)	<0·001
Mean (SD) Bmax (nmol/l cells)	8·05 (2·05)	10·96 (2·98)	<0·001



igure 1 Results of studies of red cell membrane sodium transport in the children investigated. Those with a positive family history of hypertension (n=30) re compared with those without (n=28). Bars indicate mean (SD).* For intracellular sodium concentration, n=28.*

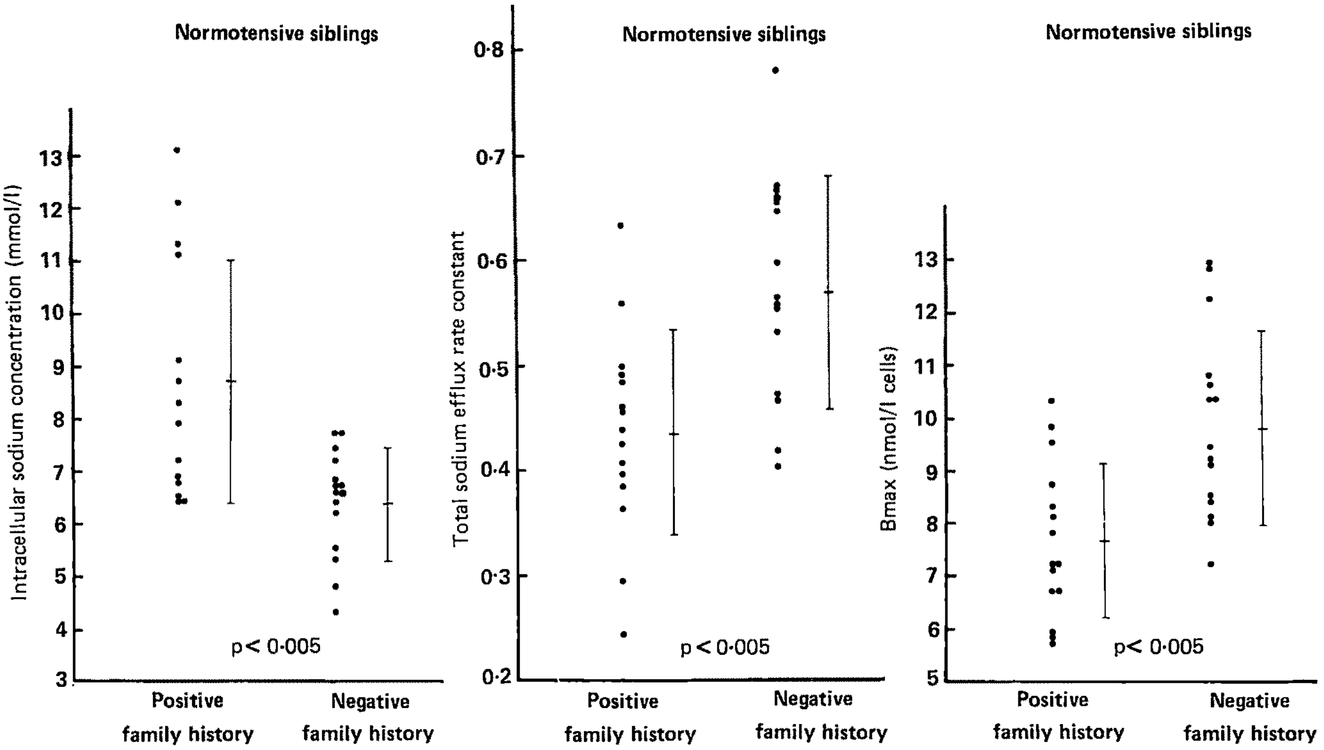


Figure 2 Results of studies of red cell membrane sodium transport in the normotensive siblings of our index hypertensive children. Those with a positive family history of hypertension (n=15) are compared with those without (n=15). Bars indicate mean (SD).* For intracellular sodium concentration, n=14.*

bed by Uchiyama *et al.*[7] All red cell membrane sodium transport assays were carried out within eight hours of venesection. Results were expressed as mean (SD) and analysis was by the unpaired Student's *t* test. A probability of <0·05 was accepted as significant.

Results

Parents who were hypertensive were compared with those who were normotensive (table 2). The hypertensive parents had significantly increased intracellular sodium concentrations, low sodium efflux rate constants, and decreased numbers of sodium/potassium ATPase dependent pump sites.

Children in the 'positive family history' group did not differ significantly from the children in the 'negative family history' group in age, blood pressure, or sodium excretion (table 1).

Children with a family history of hypertension differed significantly from those without a family history of hypertension terms of their mean (SD) intracellular sodium concentration (mmol/l cells): 8·19 (2·18) compared with 6·41 (0·98) (p<0·001); sodium efflux rate constant: 0·4873 (0·1379) compared with 0·5831 (0·1104) (p<0·01); and numbers of sodium/potassium ATPase dependent pump sites (BMax) (nmol/l cells): 7·96 (1·71) compared with 9·56 (1·7) (p<0·001) (fig 1). These data include those of the 28 index hypertensive children. To find out if the results were being influenced by blood pressure the results were reanalysed excluding the data from the 28 index hypertensive children, and comparing the normotensive siblings with a positive family history with the normotensive siblings with a negative family history; significant differences were still found (fig 2). Siblings with a positive family history had significantly increased intracellular sodium concentrations (mmol/l cells):8·7 (2·3) compared with 6·37 (1·09) (p<0·005), low sodium efflux rate constants:0·4356 (0·0970) compared with 0·5691 (0·1092) (p<0·005), and decreased numbers of sodium/potassium ATPase dependent pump sites (BMax) (nmol/l cells):7·65 (1·45) compared with 9·79 (1·82) (p<0·005).

Discussion

These results show that a family history of hypertension significantly influences sodium handling by red blood cells. Children—both hypertensive and normotensive—who had a positive family history of hypertension had raised intracellular sodium concentrations, low sodium efflux rate constants, and decreased numbers of sodium-potassium ATPase pump sites as measured by Bmax when compared with children with a negative hypertensive family history.

The abnormalities of red cell membrane sodium transport were not secondary to hypertension, abnormalities being present in the normotensive siblings of our index hypertensive children, and there was no correlation between systolic or diastolic blood pressure SD scores and any of the measures of sodium transport.

Both genetic and environmental factors play a part in the pathogenesis of essential hypertension, but so far no single underlying mechanism has been identified to explain the excessive rises in blood pressure. Blaustein hypothesised that changes in cell membranes as a result of genetic or environmental factors, or both, may account for the changes in sodium fluxes seen in essential hypertension, and that the accumulation of intracellular sodium in the smooth muscle cells of resistance vessels that results from altered sodium transport interferes with sodium-calcium exchange at the cell membrane. This causes a rise in free intracellular calcium and hence an increase in smooth muscle tone and contractility,[10] and could explain the finding of raised peripheral resistance in essential hypertension.

The familial aggregation of blood presure has been well described, and the role of heredity in its transmission has been suggested, blood pressure aggregation being the result of both a genetic component and shared environmental factors.[11–13] Studies in twins have shown that a monozygotic twin of a hypertensive subject has a substantially greater risk of being hypertensive than a dizygotic twin again suggesting an important role for heredity in the aetiology of blood pressure.[14 15] In the Montreal adoption study it was estimated that a genetic component accounted for 30% of variability in blood pressure, and that the effect of environmental factors increased with the length of cohabitation.[16] Many reports have shown that essential hypertension is more common among the relatives of hypertensive than among normotensive subjects. The risk of a child becoming hypertensive increases if both parents have essential hypertension.[17]

Some studies of abnormalities of cellular sodium transport have shown familial aggregation,[18–20] but some have shown no relationship between family history of essential hypertension and measures of sodium transport.[21] These studies used different methods, and investigated other pathways of active sodium transport across the red cell membrane; they did not investigate the activity of the sodium-potassium ATPase dependent pump. The 'children' of hypertensive parents in these studies were also older than the children that we studied, and in many of the studies the children had already developed significantly higher mean blood pressures than the control groups.

Svensson and Sigstrom studied sodium pump activity in the children of hypertensive mothers.[22] They compared children whose mothers had sustained hypertension after being hypertensive during pregnancy, children whose mothers were normotensive after being hypertensive during pregnancy, and a control group of children with normotensive mothers. They found no differences in intracellular sodium concentrations among their groups, but the children of hypertensive mothers had lower pump activity, although this was not significantly different from the children of normotensive mothers or the control group of children. Although they did not find a correlation between sodium pump activity and blood pressure, the children of the hypertensive mothers had higher blood pressures than their control groups.

Cooper *et al* investigated high school children aged 15–18 years and found significant differences in sodium pump activity between children with and without a family history of hypertension. Children with a positive family history, however, also had significantly raised diastolic blood pressures.[23]

Mongeau studied the cotransport and countertransport pathways in children, but did not find any association between a decrease in cotransport activity and a family history of hypertension. He did find, however, that an increased countertransport was associated with a familial tendency to hypertension.[24]

The abnormalities that we found are not automatically associated with increased blood pressure, and are not apparently caused by hypertension as shown by the normal results in children with secondary hypertension. They may, however, be the earliest detectable pathophysiological step in the development of raised blood pressure, and hence have some causative role. Alternatively they may just be markers, permitting the identification of children who are at risk of developing essential hypertension.

Given the large overlap in values in this study, the findings do not support the hypothesis of a monogenetic inheritance of sodium transport defects. Long term studies are required to find out if those children who have abnormal sodium transport are the hypertensive adults of the future and what environmental factors also play a part in the development of increased blood pressure.

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Predicting treatment outcome in nocturnal enuresis

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Abstract

A presenting sample of 127 consecutive referrals to a community based enuresis clinic were evaluated after treatment with baseline behavioural recording and the enuresis alarm. Almost one in five became dry after baseline recording only while 81 of 96 (84%) enuretics who used the alarm achieved the initial dryness criterion. Successful outcome was associated with the absence of adverse environmental factors and psychiatric disorders in the child. A logistic regression procedure enabled a risk score to be created so that successful outcome could be predicted. Psychiatric disorder in the child, family stress, and the degree of concern shown by the child emerged as the most important prognostic factors in the treatment of enuresis. The favourable success rates with baseline recording and the enuresis alarm confirm the role of conditioning treatment at the forefront of management of enuresis and the risk score allows outcome to be predicted for the first time.

Childhood nocturnal enuresis continues to be a common problem affecting approximately one in 10 children.[1 2] It is associated with a wide variety of disorders in the child and socioenvironmental factors in the family.[3–6] Even though enuresis causes considerable distress, many families either do not consult a doctor, or are unhappy with medical management of this problem.[1]

Treatment has revolved around pharmacotherapy or conditioning treatment such as the enuresis alarm. Tricyclic antidepressants are prescribed despite poor long term efficacy[7–9] and warnings about the dangers of side effects.[10–12] Antidiuretics (for example, desmopressin) are expensive yet no more effective than the alarm in achieving long term cure.[13]

The enuresis alarm has cure rates ranging from 30%–100%,[14 15] but there are relatively few data concerning factors that may be associated with outcome. This study aims to evaluate management of nocturnal enuresis with the alarm, identify variables relating to successful outcome, and to create a risk score thereby enabling initial and long term outcomes to be predicted.

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Subjects and methods

A presenting sample of 127 consecutive referrals to a community based enuresis clinic participated in the trial. Inclusion criteria were that the child was aged 6 to 18 years and wetting the bed at least twice a week. Exclusion criteria consisted of overt psychiatric disturbance requiring urgent referral to the child guidance service, moderate or greater mental handicap, and urological or neurological causes of incontinence. Equal numbers of referrals originated from paediatricians, general practitioners, and clinical medical officers with a smaller number from the child guidance service.

Clinics were arranged in local health centres and all children were seen initially by the medical officer (JBD), and review appointments were also seen by one of three specially trained nurses. Both the parent and child were given a structured interview to reduce interviewer bias. Information on (i) sociodemographic data, (ii) enuresis history, (iii) physical/psychiatric disorder, and (iv) family stress was elicited using a standardised chart.

(i) Sociodemographic data included age and sex of child, family size, birth order, place of residence (urban/rural), mother's and father's employment state, and social class based on an ordinal scale.[16] Housing was rated as unsatisfactory if one or more of the following was present (a) no bathroom, (b) no indoor toilet, (c) enuretic child sharing a bedroom with more than one other child, (d) enuretic child sharing a bed, and (e) house in poor repair.

(ii) Enuresis was classified as primary if the child had never acquired nocturnal continence and secondary where the child was reliably dry at night for at least six months then started wetting again. Previous treatments were listed as was the presence of diurnal enuresis. The mother was asked separately about impact on the family regarding extra washing/ironing, smell, financial consequences, reactions of other siblings, emotional impact (anxiety, fear, anger, and annoyance), and finally her concern about the problem on an ordinal scale. The child was also seen separately and questioned about the effects of enuresis on his/her life (that is, at school, the smell in the bedroom, sleeping arrangements both at and away from home, who knows about it, what are his parents expectations, what he has done to control it, and whether he can imagine himself being dry) and then to summarise his/her distress on an ordinal scale.

(iii) Physical/psychiatric disorder: a history of serious physical illness or handicap or a stressful event in early childhood was recorded (that is, hospital admission, serious accident, death of a parent, etc). Developmental delay was ascertained by inquiring about developmental milestones (sitting unsupported by 9 months, ability to walk by 18 months, inability to say linked words by 2 years, etc). Children were psychologically screened using the Rutter parental rating (A scale) of their child's behaviour.[17] Children categorised as deviant were referred for assessment to the child guidance service where the American Psychiatric Association Diagnostic and Statistical Manual III coding system for psychiatric illness was used.[18]

(iv) Family stress was coded similar to Dische *et al*[19] and included (a) anomalous parental situation where the child was not living with both natural parents, (b) marital discord where one or both parents admitted discord and the marriage was associated with past or threatened separation, (c) other family disharmony, (d) serious handicap (parents or children), (e) parental mental illness), (f) death in the immediate family, and (g) serious financial problems ascertained by inquiring about difficulties paying for heating, food, electricity, and housing rental/mortgage.

Medical screening consisted of physical examination and a midstream urine for culture and analysis. At the initial visit parental cooperation was solicited in encouraging the child to assume full responsibility for the programme. The child's confidence was gained and the reasons for being at the clinic explained. This rapport with the child was continued at all stages with he/she answering questions and being actively involved in treatment. This included behavioural procedures such as cleanliness training (cleaning self, changing bed, and ensuring clothes are left for laundry), maintaining good personal hygiene, and daily bladder exercises (bladder stretching by restraining micturition at home during the day, stream interruption, and sphincter contractions). The child was given a chart to record the wetting frequency, time and size of the wet spot, and this behavioural recording acted as a baseline control period for later evaluation of treatment. This control period lasted eight weeks during which parents and child were seen on one occasion.

The child was then assessed for alarm suitability (wetting more than twice a week) and both parent and child were carefully instructed about alarm usage (Eastleigh SM 1 with or without Pex 2 booster) as described previously.[20] Treatment was usually directed at the child with the mother instructed incidentally for supervision purposes. The child was advised to 'beat the buzzer' and treat the alarm like a friend. He/she also took responsibility for alarm testing twice weekly and the alarm procedure was explored with the child at each visit. Close supervision was maintained by regular appointments (once or twice a month), written instructions for parents, a telephone advisory service, and speedy replacement of faulty equipment.

The alarm was used until a period of 21 consecutive dry nights was achieved but if a wet night occurred during the following three weeks, the alarm was used again. Any child who relapsed after this six week dry period was offered a further course of the alarm. Outcome was assessed at two, six, and 12 months and follow up was maintained at monthly intervals until he/she was dry for three months, then at one year by post or telephone.

All data was coded for computer processing and the SAS statistical package (SAS Institute) used for χ^2 and stepwise logistic regression testing.

Results

DESCRIPTIVE

The mean age of the sample was 8·8 years (range 6–17) with a male:female ratio of 2:1. The social class distribution was socioeconomic group I (n=14, 11%), II (n=18, 14%), III (n=14, 11%), IV (n=40, 32%), V (n=32, 25%), and VI (n=9, 7%). The unemployment rate among fathers was 30% and among mothers 70%.

Enuresis was primary in 105 (83%) and secondary in 22 (17%) and most children (83%) had nocturnal enuresis only with the remainder (17%) also wetting during the day. Only two had a confirmed urinary tract infection but four had a urological abnormality. Twenty six (20%) had a stressful event in early childhood consisting of a hospital admission due to physical illness (n=21, 17%), physical handicap (n=2, 2%), serious accident (n=2, 2%), and sexual abuse (n=1, 1%). A prior attendance at the child guidance clinic was noted in 27 (21%) and comprised a reactive disorder (n=11, 9%), learning problem (n=7, 6%), mental handicap (n=4, 3%), developmental delay (n=2, 2%), personality disorder (n=2, 2%) and psychosomatic disorder (n=1, 1%).

Altogether 52 (41%) parents admitted to stress in the family. This was caused by financial difficulties (n=13, 10%), marital discord (n=11, 9%), unemployment (n=7, 6%), death in the family (n=6, 5%), other family disharmony (n=6, 5%), serious illness in the family (n=2, 2%), and combinations of the above (n=7, 6%). A family history of psychiatric illness was recorded in 11 (9%) of parents and adverse housing was coded in 23 (18%) of families. Finally parents and children were asked to rate their concern about the bed wetting; this is recorded in table 1.

OUTCOME OF TREATMENT

From 127 consecutive referrals to the enuresis clinic, 22 children became dry on baseline behavioural recording alone and did not require the enuresis alarm. One of these had relapsed when followed up at 12 months. Eight children were lost to follow up after the initial visit and one child was referred for surgical management leaving 96 children who had a trial of the enuresis alarm. Of these 81 (84%) achieved an initial successful outcome of 42 consecutive dry nights. The mean number of weeks to achieve

Table 1 Concern about enuresis

Concern	*No (%) of parents*	*No (%) of children*
None at all	3 (2)	10 (8)
A little	15 (12)	33 (26)
Moderate	56 (44)	43 (34)
A great deal	53 (42)	41 (32)

dryness with the alarm was 7·3 (range 1–26 weeks). Eleven children (12%) relapsed after the initial course of the alarm and required further treatment of which nine (82%) achieved full dryness again and the remaining two achieved more than a 50% improvement in their wetting.

Outcome was also measured at fixed time intervals of two months (baseline recording only), six months (four months after alarm), and 12 months (10 months after alarm) and is outlined in table 2. The cure rates in this table refer to children who continued to attend the clinic and if those lost to follow up are considered failures, the respective cure rates of the total number of children referred for treatment are (i) six months: all children (95, 75%), alarm group (73, 76%), and (ii) 12 months: all children (75, 59%), alarm group (54, 56%). Analysis at fixed time intervals also resulted in the cure rate at six months (four months after alarm) being less than the initial success rate because at this stage some children had relapsed while others had not yet achieved dryness but follow up at 12 months was considered an indicator of long term success.

Table 2 Treatment outcome of 127 consecutive referrals. Results are number (%) of those followed up

Outcome	*2 Months (chart only)*	*6 Months*		*12 Months*	
		All	*Alarm group*	*All*	*Alarm group*
Cure	22 (19)	95 (80)	73 (76)	75 (79)	54 (74)
Failure	96 (81)	15 (13)	15 (16)	11 (12)	10 (14)
>50% improved	—	8 (7)	8 (8)	9 (9)	9 (12)
Lost/incomplete follow up	9	9	0	32	23

Table 3 Factors associated with outcome at six months

Variable	*Presence of variable*	*Cure rate (%)*	χ^2	*p Value*
Stressful event (child)	Present	64	4·8	<0·05
	Absent	84		
Psychiatric disorder (child)	Present	58	8·5	<0·01
	Absent	85		
Family stress	Present	70	4·7	<0·05
	Absent	86		
Parental concern	None/little	50	10·1	<0·01
	Moderate/great	84		
Child's distress	None/little	47	33·6	<0·01
	Moderate/great	94		

Table 4 Factors associated with outcome at 12 months

Variable	*Presence of variable*	*Cure rate (%)*	χ^2	*p Value*
Daytime wetting	Often	0		
	Rarely	74	8·4	<0·02
	Never	82		
Urological disorder	Present	25	7·3	<0·01
	Absent	81		
Psychiatric disorder (child)	Present	47	12·7	<0·01
	Absent	86		
Developmental delay	Present	38	9·0	<0·01
	Absent	83		
Parental concern	None/little	50	6·9	<0·01
	Moderate/great	83		
Child's distress	None/little	57	11·4	<0·01
	Moderate/great	88		

Table 5 Six month outcome and risk score

Variable	*Score*	*Risk of failure*
No adverse variables	0	5%
Family stress	1	Increased by 20%
Lack of child's distress	2	Doubled
Family stress and lack of child's distress	3	Quadrupled

Table 6 Twelve month outcome and risk score

Variable	*Score*	*Risk of failure*
No adverse variables	0	One in 10
(a) Lack of child's distress	3	Increased by one quarter
(b) Developmental delay	4	Increased by one third
(c) Psychiatric disorder (child)	4	Increased by one third
(a+b) or (a+c)	7	Quadrupled
(b+c)	8	Increased fivefold
(a+b+c)	11	Increased 20-fold

VARIABLES ASSOCIATED WITH OUTCOME

The prognostic importance of several variables was examined for all children (that is, baseline recording group and alarm group) who persisted with treatment. For outcome purposes, children who achieved >50% improvement in wetting but not full cure were considered to be failures. Variables found not to be associated with outcome included place of residence (urban/rural), social class, employment state (mother or father), adverse housing, family size, child's age, sex and birth order, urinary tract infection, enuresis classification, and previous treatment for enuresis.

The significant factors associated with successful outcome at six and 12 months are shown in tables 3 and 4 respectively.

RISK SCORE

To predict outcome, a forward stepwise logistic regression procedure was performed for children attending the clinic at each of the fixed time intervals.

Six months

The variables significantly affecting outcome were stress in the family ($p=0{\cdot}02$) and the child's distress about the wetting ($p<0{\cdot}01$). When these two variables were removed from the regression equation the chance of a successful outcome at six months was 96%. A risk score was then calculated from the logistic regression procedure and allows a rapid prediction of outcome at six months (table 5).

Twelve months

The variables reaching significance were psychiatric disorder in the child ($p<0{\cdot}01$), absence of child's concern about the wetting ($p=0{\cdot}02$), and developmental delay in the child ($p=0{\cdot}03$). Without these variables, the child has approximately a nine in 10 chance of being dry at 12 months. A risk score was also calculated for the 12 month outcome (table 6). These scores are additive so that if a child has all three adverse variables, the score is $3+4+4=11$ and the risk of treatment failure is 20 times that of a child without these variables.

Discussion

Bed wetting is essentially a benign condition but it may cause a considerable amount of distress for the child and worry for the parents.[1] In this study the sample was inevitably selective as provisional admission was restricted to children older than 6 years of age and wetting at least twice a week. The pattern of referrals (secondary or tertiary) resulted in these children being considered 'difficult enuretics'. In addition, the characteristics of this study group of enuretics differed from those in a prevalence study carried out in the same area because unfavourable environmental factors were more likely to be present and a greater percentage of children tended to psychiatric disorder.[2] These findings illustrate the principle that a presenting sample of consecutive referrals such as this is not entirely representative of the general population and is more likely to represent a more severe spectrum of a disease or condition.

At the enuresis clinic two methods of treatment were offered, namely baseline behavioural recording using a combination of a 'star chart' and behavioural procedures and the enuresis alarm. The cure rate of 19% using baseline recording only is in keeping with figures described elsewhere.[21] This form of treatment increased the child's motivation, responsibility, and awareness of the problem and as this therapy was inexpensive and safe, it should be at the forefront of treatment.

The initial success rate of 84% with the alarm compares very favourably with other studies,[14 19 20 22] and may in part be due to close supervision and the child taking almost complete responsibility for the programme. The long term cure rate also remained high with almost four in five children dry one year after treatment. The fixed interval success rates refer to children who continued to attend the clinic and it is likely that many who ceased attending were failures, although Young and Morgan noted a significant percentage of non-attendance was due to the child achieving dryness or parental satisfaction with a reduction in wetting frequency.[23] It was encouraging however, that only one in 10 children relapsed after using the alarm but that with retreatment the child could expect the same chance of becoming dry as those who used the alarm for the first time.

To date, research has been limited on the question of key predictors of outcome. Demographic variables (age, sex, urban/rural, social class) and enuresis classification were unrelated to outcome, similar to that found in previous studies.[19 24] In this study the six months' success rate was significantly lowered by psychiatric disorder in the child, stress in the family, and absence of concern by the child and parents. The addition of urological disorder and developmental delay militated against long term success. While family stress has been reported previously, the link between psychological variables and outcome has been tenuous.[19 25] Fielding, however, related failure of response to diurnal enuresis,[26] and Wagner *et al* found that children rated by parents as less withdrawn and socially adequate was associated with better outcome.[8] Surprisingly adverse housing, a factor noted by Dische,[19] was not related to outcome. This may be due in part to the clinic contacting housing authorities to resolve the situation. The application of a stepwise logistic regression procedure, which enabled factors to be examined independently of each other, resulted in many of the above variables losing significance. The risk score allows prediction of outcome and it is encouraging that a child without adverse variables (table 6) can expect a nine in 10 chance of long term success. The addition of these adverse variables appreciably reduces the chance of success; this is similar to the model of Kolvin *et al*[27] with its association between outcome, sex of the child, and absence of psychiatric symptoms.

As an applicability trial this study has demonstrated that enuresis can be managed very effectively in a community based clinic. Treatment should commence with a form of star chart and behavioural procedures because of a reasonable success rate and the absence of side effects. Children failing to respond should be offered the enuresis alarm, but while success ultimately depends on the child's motivation, it is important that its use be supervised and the family receive ongoing encouragement. As a symptom enuresis requires specific treatment but a careful history may reveal a background of additional illness, family stresses, and needs and these too should be resolved to increase the likelihood of a successful outcome.

The authors thank Dr B Herity and Dr L Daly, department of community medicine, University College, Dublin, for all their advice and assistance throughout the study.

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Capillary haemangioma presenting as a lung pseudocyst

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Abstract

A girl who developed a lung cyst at 24 hours of age during gentle ventilation for respiratory distress syndrome is reported. Instead of resolving as expected of a pseudocyst it continued to expand. Resection at 1 year of age showed a cyst entirely surrounded by capillary haemangioma. Aspiration of this cyst would have been dangerous.

Pulmonary pseudocyst formation is a recognised complication of ventilation in neonates with respiratory distress syndrome. We report an infant where the cyst did not resolve as expected.[1]

Case report

A girl of 30 weeks' gestation and birth weight 1200 g was born by emergency caesarean section for abruption. Dates were confirmed by an early scan and the pregnancy had been normal until slowing of fetal growth at 28 weeks. She was intubated and ventilated for five minutes initially and reintubated at 15 minutes for recession and cyanosis in 60% oxygen.

Blood gas concentrations were satisfactory and peak pressures no higher than 16 cm H_2O were used for ventilation. Hypotension was treated with fresh frozen plasma. The first chest radiograph showed mild hyaline membrane disease, and the second at 18 hours showed the first suggestion of a bulla in the apex of the right lower lobe posteriorly in association with a right pneumothorax, which was drained (fig 1A). The air leak continued for five days, and she was extubated on the sixth day and the drain removed on the seventh. Serial radiographs showed pulmonary interstitial emphysema and a progressive increase in the size of the bulla (fig 1B). She remained somewhat tachypnoeic and required oxygen until the 57th day. At three months of age she developed a capillary haemangioma on the scalp and one on the buccal mucosa but she has not had any telangectasia.

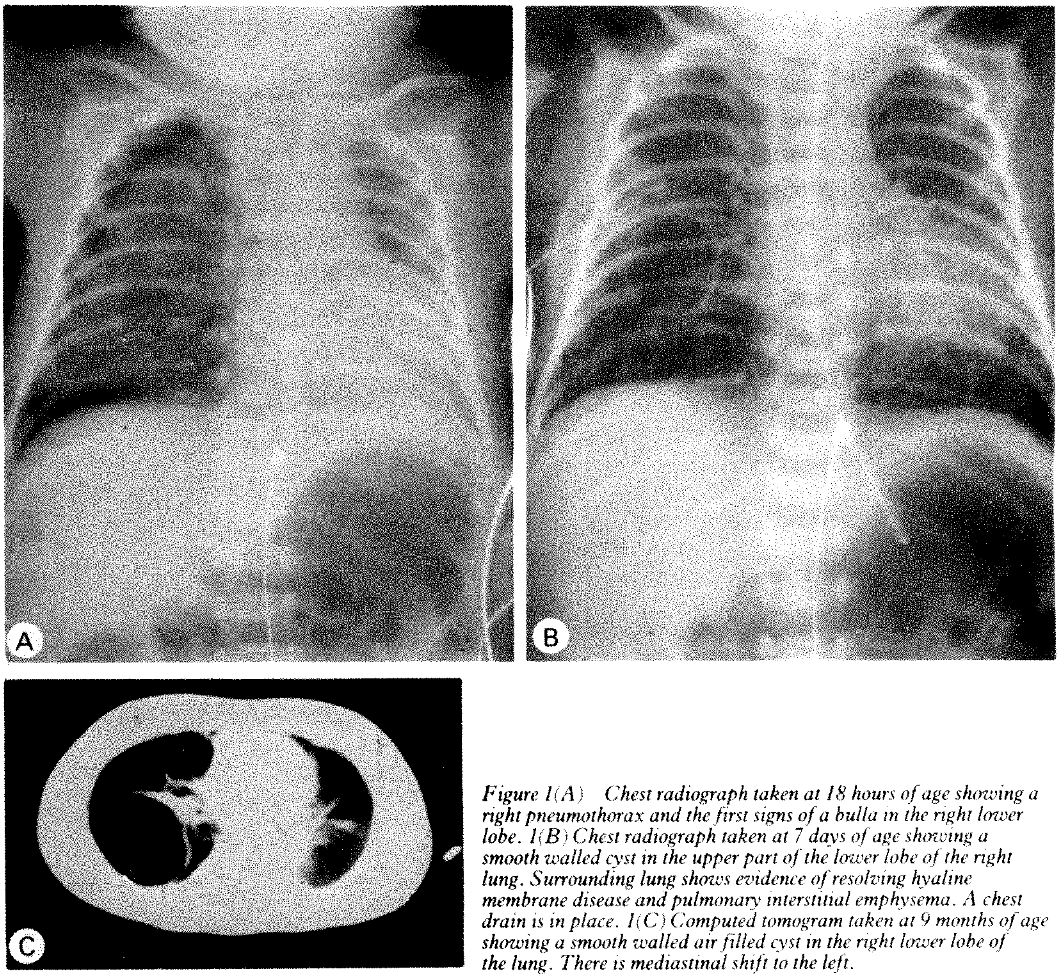

Figure 1(A) Chest radiograph taken at 18 hours of age showing a right pneumothorax and the first signs of a bulla in the right lower lobe. 1(B) Chest radiograph taken at 7 days of age showing a smooth walled cyst in the upper part of the lower lobe of the right lung. Surrounding lung shows evidence of resolving hyaline membrane disease and pulmonary interstitial emphysema. A chest drain is in place. 1(C) Computed tomogram taken at 9 months of age showing a smooth walled air filled cyst in the right lower lobe of the lung. There is mediastinal shift to the left.

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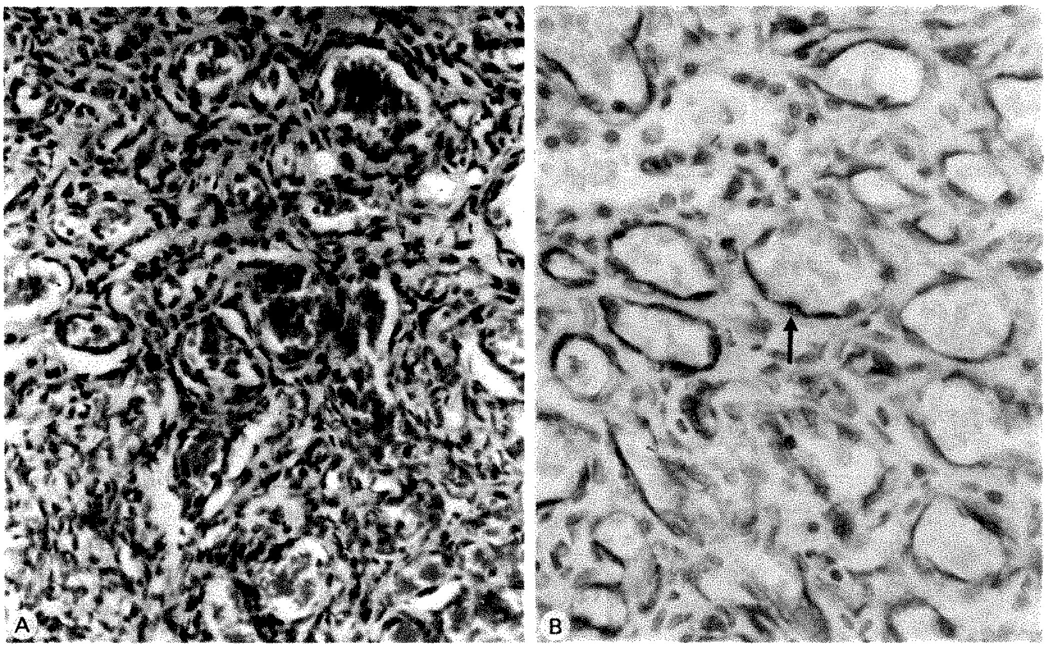

Figure 2(A) Wall of cyst containing multiple capillaries lined by endothelial cells (stained with haemotoxylin and eosin×400). 2(B) Capillaries lined by endothelial cells immunoreactive for factor VIII (arrow) (avidin-biotin complex method×400).

At 9 months computed tomography showed a tense cyst in the right lower lobe which was compressing the right upper lobe and causing mediastinal shift (fig 1C). There was a second, smaller cyst just to the left of the hilum and consolidation of the left lower lobe. A ventilation-perfusion scan showed a matched deficit corresponding to the cyst but no abnormality of vascular supply.

At operation at 1 year a tense intrapulmonary cyst, 6 cm diameter, distended the right lower lobe and spread onto both hilar and lateral surfaces encircling the hilar structures. The vascular connections of the lung were normal. The right lower lobe was resected but the cyst on the left was not explored.

HISTOPATHOLOGY

The specimen received was a segment of the right lower lobe of the lung measuring 8·5×5 ×2·5 cm with a previously incised cyst measuring 3 cm in the collapsed state. The cyst wall was smooth with some fibrous thickening in areas and was completely surrounded by lung parenchyma. No vascular or bronchial connection to the cyst could be seen. Microscopic analysis showed that the cyst wall was composed largely of multiple capillaries lined by plump endothelium (fig 2A), which stained positively for factor VIII related antigen (fig 2B). Capillaries varied in size, some were collapsed, others filled with blood. The inner lining of the cyst contained fibrous tissue but no respiratory or gastrointestinal epithelium and no mitotic activity was seen. Giant cell reaction, which might be expected in interstitial emphysema, was not seen. The capillaries infiltrated the surrounding lung irregularly for a short distance but the parenchyma appeared normal with no diffuse involvement by the angioma. A diagnosis of capillary haemangioma was made.

Discussion

Pulmonary pseudocyst formation is a recognised complication of ventilation in neonates with respiratory distress syndrome. Such cases are associated with the development of interstitial emphysema, pneumothoraces, and later bronchopulmonary dysplasia.[1] Thus our initial impression in this case was that the cyst was a ventilation induced pseudocyst that would be expected to resolve spontaneously.

The increasing size of the cyst and evidence of compression of the surrounding lung led to the decision to remove the affected lobe. The finding of a capillary haemangioma entirely surrounding the cyst was unexpected and has not previously been reported.

True congenital lung cysts are usually either bronchogenic cysts, which are lined with respiratory epithelium, enteric cysts lined with gastrointestinal epithelium, or cystic adenomatoid malformations.[2] These are characterised by cysts and bronchioles lined by ciliated columnar epithelium and goblet cells, and may become malignant.[3] Even apparently simple congenital lung cysts may be associated with abnormal vasculature, either systemic arterial supply or anomalous venous return, and require full evaluation before surgery is planned.[4]

Vascular malformations in the lung are generally cavernous haemangiomata with large channels of communication between pulmonary arteries and veins, commonly associated with hereditary haemorrhagic telangectasia.[5] True capillary haemangiomata occurring in the bronchial submucosa may give rise to severe haemoptysis.[6] One comparable case of vascular channels lying in the substance of the lung in association with an expanding cyst was reported in a 25 year old man, but there the cyst was lined with respiratory epithelium.[7]

Our finding of a capillary haemangioma totally surrounding a lung cyst appears to be new. Aspiration of pseudocysts in ventilated neonates has been advocated,[8] but in the present case that might have been disastrous. In view of the known association of congenital parenchymal and vascular abnormalities,[4] and in the light of this experience, we would recommend full evaluation of all cysts before planned surgery.

We are grateful to Dr J Warner and Mr P Goldstraw for permission to report the patient in their care.

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Forty years ago

Infantile cortical hyperostosis (Caffey's syndrome)

Caffey, an eminent American paediatric radiologist, was the first to describe a syndrome occurring mainly in the first six months of life and characterised by tender soft tissue swellings and cortical thickening of the underlying bones.[1]

The first case of Caffey's syndrome to be reported in the United Kingdom was a 2 month old baby boy who was admitted to hospital with a one week history of swelling of the face and fever.[2] On examination there were moist sounds in the right lung and a tender swelling of the left side of the face. He was given antibacterial treatment without improvement; the fever persisted and after 10 days he was noticed to have generalised lymphadenopathy and a tender swelling over the shaft of the left humerus. Over the next few days similar swellings developed over the right ramus of the mandible, both radii, and both tibiae. Radiographs of the long bones, ribs, pelvis, and mandible showed periosteal elevation and irregular new bone formation. Blood examination showed an anaemia with polymorphonuclear leucocytosis and the blood chemistry was normal apart from a raised alkaline phosphatase. There was no evidence of syphilis, tuberculosis, or scurvy. A biopsy specimen of the left tibia showed proliferation of osteoblasts but no evidence of infection or malignancy. The clinical signs gradually subsided over the next three months, and one year after the onset the child was well and the radiographs showed a return to normal.

Thrush in infancy

In a 12 month period in Liverpool necropsies were carried out on 204 infants under the age of 1 year, of whom 28 were aged less than 4 weeks. In seven (25%) of the neonates and 19 (11%) of the older infants pharyngeal or oesophageal lesions of thrush were found and were considered directly or indirectly responsible for the death of the child.[3] Of the 26 infants with thrush only three had been breast fed and only two were of low birth weight. The commonest clinical features on admission were oral lesions of thrush, vomiting with or without diarrhoea, and severe dehydration. Otitis media developed later in 10 cases, in four of which *Monilia albicans* (now *Candida albicans*), was found on smear or culture.

At postmortem examination 21 of the 26 infants were found to have oesophageal lesions of thrush, some with ulceration or sloughing. Eleven had histological evidence of inhalation of vomit with aspiration pneumonia and six had died suddenly due to obstruction of the airways by aspirated material. In two infants infection had spread from the oesophagus to the pleural cavity causing an empyema. Pyaemic abscesses, which were presumed to have originated in the ulcerated oesophagus, were found in various organs in five cases. In two there were metastatic thrush lesions in the kidneys. Ulcerated areas in the intestine were present in four cases but only in one of these was this proved to be due to thrush.

The authors warn that thrush may pass unnoticed at necropsy unless histological examination is undertaken, as the macroscopical appearances may be non-specific. In their view the histology suggests that monilia is the primary infection and that the damaged epithelium is invaded by bacteria, rather than the monilia being an opportunistic secondary invader of a primary bacterial lesion.

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A D M JACKSON

Benign intracranial hypertension after ciprofloxacin administration

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Abstract
Many drugs, including antibiotics, have been implicated in the aetiology of benign intracranial hypertension. We report the development of benign intracranial hypertension after the use of ciprofloxacin in a teenager with cystic fibrosis.

Benign intracranial hypertension has been linked with several different aetiological factors. Many of these implicate drugs, particularly antibiotics,[1] in the development of benign intracranial hypertension. The girl with cystic fibrosis presented in this case report had been treated with an antipseudomonal antibiotic not previously associated with benign intracranial hypertension.

Case report

A 14 year old girl with cystic fibrosis presented with a 10 day history of headache and vomiting. Her headache resolved after two days, although her nausea and vomiting persisted. She also complained of intermittent diplopia. Despite the diagnosis of cystic fibrosis, her general health and respiratory function were well maintained. Recent recurrent chest symptoms had been initially treated with cefaclor then changed to ciprofloxacin after 10 days because of a poor response to the former antibiotic. Her current medication also included pancreatin, vitamin supplements (Ketovite, Paines and Byrne), carbohydrate supplements (Maxijul, Scientific Hospital Supplies), with ciprofloxacin 250 mg twice daily.

Examination showed a well nourished girl continuing her growth pattern with her height on the 50th centile and weight on the 10th centile. A left VIth cranial nerve palsy and bilateral papilloedema were noted. Visual acuity was reduced to 6/9 on the left. Perimetry did not demonstrate a visual field deficit. There was no evidence of meningism, ataxia, or cerebellar dysfunction. She was normotensive. Respiratory examination showed a mildly hyperexpanded thorax with scattered inspiratory crepitations. There was evidence of early puberty. She was transferred to the neurosurgical department of the Hospital for Sick Children, London.

Plasma electrolyte estimations were normal. Cranial computed tomography showed ventricular compression without cerebral oedema or space occupying lesion. Lumbar puncture showed normal cerebrospinal fluid at a raised pressure of 41 cm cerebrospinal fluid (normal range 7–18). A diagnosis of benign intracranial hypertension was made. At that stage, erythromycin was substituted for ciprofloxacin, on the assumption that ciprofloxacin was the only recent change in treatment and therefore the likely cause of the problem. Two further lumbar punctures were performed which showed persistently raised cerebrospinal fluid pressures each treated with removal of 10 to 25 ml of fluid. There was subsequent symptomatic improvement with resolution of the cranial nerve palsy but with residual papilloedema. Further lumbar puncture three weeks later showed a pressure of 23 cm cerebrospinal fluid, which was treated with removal of a further 25 ml of fluid. There was further resolution of the papilloedema and the nerve palsy did not recur.

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Discussion

Benign intracranial hypertension was initially associated with impaired cerebrospinal fluid absorption resulting from lateral sinus thrombosis after acute otitis media, hence the term 'post otitic hydrocephalus'.[2] It has also been associated with 'catch up' growth in cystic fibrosis after a period of relative malnutrition.[3] In this case, however, the growth pattern had been well maintained. Various drugs have been implicated including tetracyclines[4] and nitrofurantoin.[5] We are unaware of any previous reports linking the administration of the 4-quinolone antibiotic ciprofloxacin and benign intracranial hypertension. Since this report was submitted, we are aware of a recent additional case occurring in an adult in the USA during ciprofloxacin treatment for sinusitis (personal communication, Bayer UK Ltd). Such an association has been documented with the use of nalidixic acid,[6] which is the parent compound for the quinolone series of antibiotics. The above association is important because of the increasing popularity of the quinolone group of antibiotics and their use as oral antipseudomonal agents particularly in those with cystic fibrosis. Ciprofloxacin is being advertised for use in general practice for many infections. It has been extensively used in cystic fibrosis for pseudomonas infection. With increasing use there is a possibility of developing a resistant organism and benign intracranial hypertension should be considered if headache is a new symptom.

We would like to thank Mr DN Grant and his neurosurgical colleagues at the Hospital for Sick Children, Great Ormond Street, London, for their help in the management of this patient.

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5α–Reductase deficiency without hypospadias

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Abstract

A boy aged 4 with penoscrotal hypospadias and his brother aged 12 with micropenis had typical changes of homozygous 5α-reductase deficiency. After three injections of chorionic gonadotrophin there was a trivial rise in plasma dihydrotestosterone with a normal increase in plasma testosterone. Urine steroid chromatography showed abnormally high 5β: 5α ratios and 5α-reductase activity was appreciably reduced in genital skin fibroblasts. The results indicate that 5α-reductase deficiency is not invariably associated with genital ambiguity.

5α-Reductase deficiency is a well recognised but uncommon cause of male pseudohermaphroditism.[1] Published cases have been characterised by pronounced underdevelopment of the male external genitalia with microphallus and incomplete fusion of the labioscrotal folds.[2] Many of the reported cases have been initially raised as girls because of the female appearance of the genitalia at birth but cases with more pronounced virilisation have been described.[3]

All previously reported males with 5α-reductase deficiency have had some degree of genital ambiguity with hypospadias. We describe two brothers with the condition, one of whom had micropenis without hypospadias while the other had penoscrotal hypospadias.

Patients and methods

The propositus and his older brother had consanguineous parents who come from Pakistan. At birth, the younger boy was found to have abnormal external genitalia with a small phallus and hypospadias. When he was 4 years old he was referred for evaluation of his genital anomaly. At that time he was noted to have a small penis (stretched length 1·9 cm) with noticeable chordee and penoscrotal hypospadias. The scrotum was normal but only the right testis was palpable.

Initial investigations showed a 46XY karyotype. A sinogram showed a normal bladder; the proximal urethra had a male configuration with a prominent vermontarum and well developed utricle.

After initial evaluation he was given one injection of depot testosterone (50 mg) to improve the size of his penis and hypospadias repair was carried out. A skin biopsy specimen for fibroblast culture was taken at that time.

The older brother was noted to have a small penis at birth. He was seen at the age of 12 years, at the same time as his brother. His external genitalia were normal, apart from the size of his penis, which had a stretched length of 4 cm. There was no chordee and the urethra opened at the tip of the penis. Both testes were in the scrotum and were 6 ml in volume.

Investigation showed a 46XY karyotype. After initial investigation a skin biopsy specimen was obtained from the scrotum.

Plasma testosterone and dihydrotestosterone concentrations were measured by radioimmunoassay before and after three daily injections of 1000 units of human chorionic gonadotrophin. Urine steroid concentrations were measured by gas chromatography as previously described,[4] and the results expressed in terms of 5β:α ratios for different steroid metabolites.

Fibroblasts were established in culture from genital skin to determine 5α-reductase activity and androgen receptor concentrations. The activity of 5α-reductase was measured after incubation of fibroblasts with serum free medium containing 2 nM of tritiated testosterone. The medium was extracted with ethyl acetate and analysed by single step thin layer chromatography. Areas corresponding to dihydrotestosterone, 5α-androstanedione, androsterone, epiandrosterone, and the 5α-androstanediols were cut out and counted for tritium. Enzyme activity was expressed in pmol/mg protein/hour of 5α-reduced products. The concentration of androgen receptors, receptor binding affinity, presence or absence of heat labile receptors, and effect of preincubation

Table 1 Results of endocrine investigations

	Propositus	*Brother*
Before human chorionic gonadotrophin:		
Testosterone (nmol/l)	0·4	3·1
Dihydrotestosterone (nmol/l)	0·1	0·2
Testosterone:dihydrotestosterone ratio	4·0	1·5
After human chorionic gonadotrophin:		
Testosterone (nmol/l)	4·2	21·9
Dihydrotestosterone (nmol/l)	0·1	0·3
Testosterone:dihydrotestosterone ratio	42·0*	73·0*
Urinary 5β:5α ratios:		
THF:*allo*THF†	24·7	14·3
Aetiocholanolone:androsterone‡	0·6	4·7
THB:*allo*THB§	0·8	4·3

*Normal range in prepubertal boys:2–25.[1]
Mean (SD) results in normal subjects: †1·1 (1·7), ‡0·8 (1·7), §0·7 (1·6).

Table 2 5α-Reductase activity and androgen receptor concentrations in genital skin fibroblasts. Values in 22 normal subjects are also given

	Propositus	*Brother*	*Normal subjects*
5α-Reductase activity (pmol/mg protein/hour)	0·5	0·6	12·8 (range 3·3–42·3)
Androgen receptor concentration ($\times 10^{-18}$M/μgDNA)	815	939	775 (SD 185)
Receptor binding affinity ($\times 10^{-10}$M)	0·82	1·09	0·88 (SD 0·35)
Thermolabile	No	No	No
Augmentation	×2·6	×1·8	×1·4

with androgen on receptor concentrations (termed 'augmentation') were determined as described previously.[5, 6]

Results

The results of endocrine investigations are summarised in the tables.

PLASMA ANDROGENS

Both boys showed a rise in plasma testosterone after stimulation with human chorionic gonadotrophin, which was appropriate for their ages. There was a trivial increase in dihydrotestosterone and this resulted in extremely high testosterone:dihydrotestosterone ratios in both boys after human chorionic gonadotrophin (table 1).

URINE STEROIDS

Both brothers showed an abnormal pattern of urinary steroid metabolites, with high ratios for 5β:α reduced steroids (table 1). This was most striking in the tetrahydrocortisol:*allo*tetrahydrocortisol (THF:*allo*THF) ratio, which was 24·7 in the propositus and 14·3 in his older brother. In normal adult males the mean (SD) ratio is 1·1 (1·7). The ratios for aetiocholanalone:androsterone (4·7) and tetrahydrocorticosterone:allotetrahydrocorticosterone (THB:*allo*THB) (4·3) were also raised in the propositus. In his brother the aetiocholanalone:androsterone and THB:*allo*THB ratios were normal and this is probably related to the low concentrations of these metabolites before puberty.

SKIN FIBROBLAST STUDIES

Fibroblast 5α-reductase activity in both brothers was extremely low at 0·5 and 0·6 pmol/mg protein/hour, as compared with a mean of 12·8 pmol/mg protein/hour (range 3·3–42·3) in eight normal males (table 2).

Androgen receptor concentration was normal in both brothers at 815 and 939×10^{-18} M. There was no evidence of receptor thermolability, and receptor augmentation after preincubation with androgen was normal.

Discussion

The biochemical findings described above indicate that both brothers are homozygous for 5α-reductase deficiency. Not only was there no significant rise in plasma dihydrotestosterone after human chorionic gonadotrophin stimulation but very abnormal THF:*allo*THF ratios were obtained on urine chromatography. 5α-Reductase activity in fibroblasts grown from genital skin was extremely low, findings which are typical of homozygous 5α-reductase deficiency.

5α-Reductase deficiency usually produces severe male genital ambiguity with bifid scrotum, urogenital sinus, and a clitoris like phallus,[1, 2] but three brothers with labioscrotal fusion and hypospadias have been described.[3] The absence of hypospadias in our older patient is very much in contrast with all previously reported cases of 5α-reductase deficiency, and it is very difficult to account for the absence of hypospadias in the light of current views on male external genital development. During early fetal development testosterone is thought to act as a prohormone in the urogenital tissues where it is converted to dihydrotestosterone by intracellular 5α-reductase, thus effecting virilsation of the external genitalia. Penile growth is at least partly dependent on intracellular 5α-reductase as micropenis has been a cardinal feature of all reported cases of 5α-reductase deficiency.

Our findings indicate that there may be considerable heterogeneity in the clinical manifestations of 5α-reductase deficiency. In the older case, sufficient local dihydrotestosterone must have been produced to allow early virilisation of the genitalia with fusion of the labioscrotal folds to produce a normal urethra and scrotum. In the younger boy, virilisation was slightly less complete leading to penoscrotal hypospadias and chordee. Reduced 5α-reductase activity in the second half of gestation probably accounts for the presence of microphallus at birth.

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Indomethacin responsive hypercalcaemia associated with a renal sarcoma

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Abstract

An infant presented with a non-metastatic renal spindle cell sarcoma and hypercalcaemia, which resolved after treatment with indomethacin. There was in vivo and in vitro evidence that hypercalcaemia was mediated by circulatory prostaglandins.

In adults, tumour derived polypeptides such as tumour necrosis factor, interleukin-1, transforming growth factor alpha (TGF-α) and parathormone related peptide (PTHrP) have been shown to act as tumour derived humoral mediators of hypercalcaemia.[1] A similar role has also been proposed for prostaglandins but overall results of treatment with prostaglandin inhibitors have been disappointing.[2]

'Humoral' hypercalcaemia only rarely accompanies malignancy in childhood, and tends to occur with unusual tumours.[3] We report the case of an infant with a prostaglandin producing renal sarcoma and hypercalcaemia responsive to indomethacin.

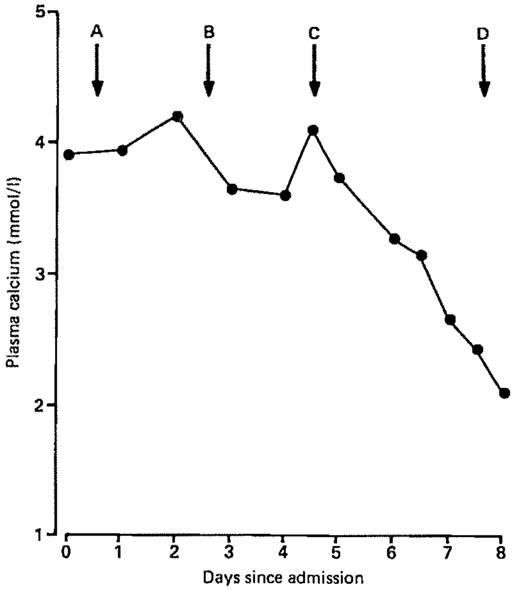

Figure 1 Serial plasma calcium measurements: (A) intravenous hydration started, (B) frusemide started, (C) indomethacin started, and (D) nephrectomy. After nephrectomy serum calcium remained normal.

Case report

A 6 month boy presented with irritability and poor appetite for one month. His mother had noticed an abdominal swelling a week previously. On examination he was pale and had moderate abdominal distension due to a large, right sided abdominal mass. Haemoglobin concentration was 91 g/l, white cell count 19·4×10^9/l with a normal differential and platelets 580×10^9/l. Plasma urea concentration was 7·9 mmol/l and creatinine 63 μmol/l. The plasma calcium concentration was raised at 3·91 mmol/l, with normal concentrations for plasma albumin (37 g/l) and phosphate (1·40 mmol/l) and alkaline phosphatase activity (268 U/l). Serum total parathyroid hormone was 180 ng/l (normal range for age 120–380 ng/l), and 25-hydroxyvitamin D 52·9 nmol/l (normal range for age 7·5–75·0 nmol/l). Chest radiography showed a raised right hemidiaphragm with some associated basal collapse, but no lung metastases. Renal ultrasound demonstrated a large, partly cystic right renal mass. Computed tomography showed that the mass crossed the midline in front of the aorta and extended down into the pelvis. Skeletal survey was normal.

Intravenous hydration was commenced, then frusemide added. After four days the hypercalcaemia persisted (fig 1) so indomethacin was administered (2 mg/kg/day in four divided doses). Over the next three days the plasma calcium fell to within the normal range, before surgery (fig 1). At operation, only a small amount of normal renal tissue lay stretched over the upper pole of the tumour. Right nephrectomy was performed, the excised specimen weighing 1035 g. Histological examination showed a malignant tumour composed of undifferentiated spindle shaped cells with a high mitotic count, interspersed with loose myxoid mesenchymal areas. Extensive foci of necrosis were present and tumour eroded the surrounding pseudocapsule in several areas. Immunohistochemical studies showed positive vimentin staining in the tumour cells only and electron microscopic appearances were non-specific. No histological or ultrastructural evidence of malignant rhabdoid tumour was present. The tumour was therefore classified as an 'undifferentiated sarcoma'.

After nephrectomy, a nine month course of combination chemotherapy (pulses of vincristine, actinomycin D, and cyclophosphamide alternating with etoposide, vincristine, and doxorubicin) was given. One year after completion of treatment the child remains well, normocalcaemic, and free from tumour recurrence.

Methods

Fragments of tumour (1 mm^2) were incubated for three days in 25 cm^2 flasks (Sterilin) each with 5 ml of Eagle's modified essential medium (Gibco). Medium was then removed and half

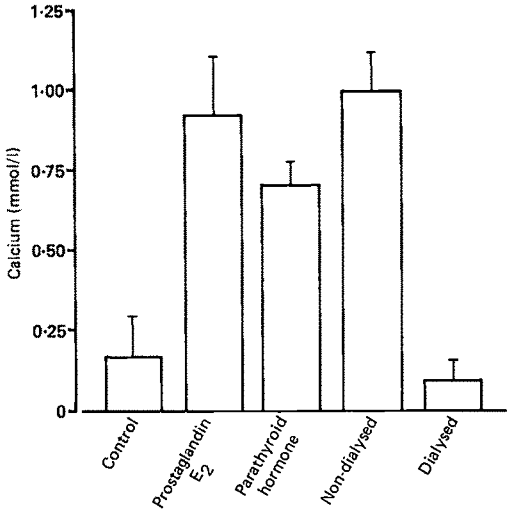

Figure 2 Effect of non-dialysed and dialysed tumour explant supernatants (1:10 dilution) on bone resorption in vitro. Positive controls were prostaglandin E_2 *(10^{-6} M) and parathyroid hormone (10^{-8} M). The difference between results with dialysed and non-dialysed samples is significant ($p=<0{\cdot}05$; Student's t test).*

was dialysed using benzolyated dialysis tubing (cut off point 2000 molecular weight; Sigma). In vitro bone resorption was assayed by colorimetric measurement of calcium release from five day old mouse calvaria, incubated for 48 hours with control media and with tumour media (both dialysed and non-dialysed.)[4] Prostaglandin E_2 was measured by radioimmunoassay: tritiated prostaglandin E_2 was obtained from Amersham International UK, antiserum from Steranti, and standards from Sigma.

Results

Before indomethacin treatment the concentration of urinary prostaglandin E_2 was 1034 pg/mmol creatinine. During indomethacin treatment it fell to 609 pg/mmol creatinine, coincident with a reduction in plasma calcium (fig 1). At nephrectomy, before ligation of the vessels, the renal arterial:venous prostaglandin E_2 concentrations were 500:2000 pg/ml. The renal tumour contained 56 ng prostaglandin E_2/mg wet weight compared with 1·0 ng prostaglandin E_2/mg wet weight of normal renal tissue.[4]

The undialysed tumour explant medium caused significant in vitro bone resorption (fig 2), comparable with the media containing either prostaglandin E_2 or parathyroid hormone. In contrast, the dialysed sample of the same medium caused no bone resorption indicating that the active molecule was <2000 molecular weight (the molecular weight of prostaglandin is 300–500).

Discussion

Hypercalcaemia in malignancy may result from either the release of calcium from sites of widespread bone metastasis or from the release of tumour derived humoral factors that cause panskeletal bone resorption. In the absence of evident bone metastases, a humoral cause for our patient's hypercalcaemia seemed likely. Humoral hypercalcaemia has been reported in association with two rare types of childhood renal tumours: mesoblastic nephroma and malignant rhabdoid tumour. Some tumours have been shown to produce either prostaglandin E_2[4 5] or parathyroid hormone.[6] However, there are no previous reports of the use of prostaglandin inhibitors in management.

The role of circulating prostaglandin in the production of malignancy associated humoral hypercalcaemia is still controversial.[1] Prostaglandins and their metabolites have short plasma half lives and may act indirectly by stimulating other cells to release bone resorbing factors. In our patient there was strong evidence that prostaglandin E_2 was involved in the pathogenesis of the hypercalcaemia. Firstly, the tumour contained significant amounts of prostaglandin E_2 and caused bone resorption in vitro. Secondly, there was a substantial arteriovenous gradient across the tumour. Thirdly, the patient's serum calcium concentration fell to normal after the administration of indomethacin, with the tumour still in situ, coincident with a reduction in urinary prostaglandin E_2 excretion.

To our knowledge, this is the first report of hypercalcaemia associated with a non-metastatic sarcoma in childhood, and is in line with previous observations that this is a complication of unusual childhood tumours. The evidence that prostaglandin E_2 was implicated in its pathogenesis, and the clinical response to indomethacin, provide a treatment alternative for future similar cases of tumour associated humoral hypercalcaemia.

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CURRENT TOPIC

Paediatric medical audit

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According to the Royal College of Physicians report 'Medical audit is primarily a mechanism for assessing and improving the quality of patient care; enhancing medical education by promoting discussion between colleagues about practice; identifying ways of improving the efficiency of clinical care'.[1] Other definitions exist: 'Medical audit is a systematic approach to peer review of medical care in order to identify opportunities for improvement and provide a mechanism for realising them. Medical audit and clinical audit are often used interchangeably, but clinic audit might be considered to cover all aspects of clinical care—eg nursing and the role of paramedical staff—whereas medical audit relate to practices initiated directly by doctors. It complements and may partly overlap financial audit, utilisation review and management of resources, but is primarily clinical, not managerial. The focus is the process and results of medical care rather than the use of resources and it is the responsibility of doctors rather than managers'.[2]

Purpose of medical audit

Medical audit is primarily an educational exercise for doctors intended for the benefit of the patient. Some monitoring of the use of resources including medical time will result, as well as an assessment of the disturbance to the child and to his or her family resulting from illness and medical intervention. A secondary gain may be more efficient use of limited health care resources.

Uncertainties in paediatric medical audit

Clinicians see medical audit as primarily a medical responsibility, although this view is not universally shared. The Royal College of Physicians Working Party saw medical audit as a professional activity preserving clinical freedom within a healthy atmosphere of challenge between clinicians, leading to improvement and development of clinical practice but with benefits to the patient, family, and to the population as a whole by more efficient use of resource.[1] Medical audit activities may also provide justification for the development of new techniques or expenditure to improve care. These principles are generally acceptable to clinicians but the implications of the white paper *Working for Patients*[3] prove more worrying: where clinical freedom may be perceived to be challenged and clinicians exposed to medicolegal retribution or painful criticism, especially from nonprofessional groups who may not understand the circumstances in which practice occurs. The white paper recommends that managers request regular audit of clinical practice. Clinicians are concerned that as this expands into process and outcome areas comparisons will be made by managers between and within districts and regions.

It is important to compare like with like and the data will require careful evaluation by clinicians and epidemiologists to exclude errors of input or variations due to local populations or circumstances before attributing differences to personal performance. As it appears likely that in the future directors of public health will advise district health authorities on where to place contracts on the basis of such audit information it behoves clinicians to take an interest in data collection from an early stage.

Confidentiality

The clinical information gathered during medical audit sessions should be confidential and kept separately from the clinical records. Management should facilitate audit by clinicians who in turn should, within the limits of confidentiality, facilitate managerial review especially when relating to structure and resource.

Methods of paediatric medical audit

Medical audit lies within the framework of 'Structure', 'Process', and 'Outcome'.

(A) STRUCTURE

Structure involves the quantity and type of resources available and is usually easy to measure, set standards for, and change. It is not usually a good indicator of the quality of care but its review may provide explanations for poor quality of delivery of care. Standards need to be set against which provision of resources may be judged.

Examples include: (1) Guidelines for medical staffing at senior and junior level for districts (The British Paediatric Association (BPA)) and provision of nursing and medical staff for neonatal care.[4] (2) Nurse staffing related to ward size and dependency[5] and A Woodhouse, Recommended staffing levels for a 20 bedded/cot children's ward in a district general hospital. Newsletter of the Society of Paediatric Nursing, Royal College of Nursing, 1989. (3) Bed numbers for children with occupancy rates low enough to prevent children being admitted to adult wards (no adequate data available but a health building note advised 75% occupancy with approximately 1 bed/1000 child population).[6] (4) The facilities and staffing which should be available for children receiving care in the health service available from the BPA and summarised in the *Quality Review* published in 1989 by the National Association for the Welfare of Children in Hospital.[7]

Future developments could include guidelines for the number of outpatient clinics per week that a consultant might be expected to undertake. In assessing the number of children per clinic note will have to be taken of the type(s) of disorder encountered and the experience and number of supporting junior staff, with recognition that too high a number may be associated with a lesser quality of care, and that for certain conditions very small clinics are appropriate.

(B) PROCESS

Process audit can include the assessment of access to paediatric services, such as the waiting time to be seen in a new patient clinic for a common condition. In acute conditions delay in referral or lack of referral may be monitored and problems may relate to the resource provision (for example number of beds, staff, or clinics) or to clinical judgment. The British Association of Perinatal Medicine has data on the difficulty in achieving access to regional neonatal intensive care units for newborn babies and this could be used as a basis for audit of services. These access evaluations inevitably overlap structure audit.

Process audit, however, mainly relates to the way in which a patient was managed and the specialty of paediatrics needs to establish management guidelines for a number of common conditions which can be used for *between* hospital comparisons. For the less common conditions paediatric subspecialists could collaborate with paediatricians from district hospitals to provide a commonsense consensus of approach. Furthermore, guidelines must be recognised as just that and clinicians should be able to diverge from them when judged necessary. Such safeguards in the implementation of guidelines will protect individual clinical freedom and safeguard the principle that clinicians will have differing styles of practice. Audit meetings will not only look to see how actual practice matches up these agreed guidelines but also whether the process itself is providing effective care.

Part of procees audit is the system of case note review which involves such a monitoring exercise and contributes to the quality of care, communication, and record keeping. It is such case note reviews that the Royal College of Physicians has proposed that visiting teams evaluating training posts should examine. Examples given in the Royal College of Physicians report (appendix 1 and 2)[1] have been modified for paediatrics at Pinderfields Hospital and are available from RM. The BPA Paediatric Audit Working Party will produce more suitable forms for general use by autumn 1990. The quality of clinical assessment of children, communication with parents, family doctors, community child health services, etc, and the use of laboratory resources as well as the management of common or rare conditions can be examined during such case note reviews.

Problems raised in the provision of services could be discussed at intervals with local managers who may wish to compare local performance with regional and national figures. If this is the case it is important to appreciate that special local conditions may often preclude meaningful comparison.

A potential disadvantage of process audit is increased standardisation of practice, although the accompanying decrease in the extremes of style of practice may be generally welcomed.

(C) OUTCOME

Medical audit is focused heavily on structure and process while useful information about outcomes is still awaited. The BPA Outcome Measures Working Party has produced a helpful initial report.[8]

Clinical information systems

All audit systems will require data recording and retrieval for the purpose of providing useful information. Resource management initiative sites will be the first to benefit from computerised systems, which ideally should extend across hospital and community child health services.

(A) DATA COLLECTION

Data collection systems and diagnostic codes used in district hospitals in the United Kingdom and the rest of Europe should be similar so that in future meanful comparisons can be made about care provision in different areas. These systems need to be compatible with existing ones dealing with obstetric, neonatal, and community child health data in order to avoid collecting the same information more than once and to promote sharing of information between departments. It should be possible to record information onto the systems easily with terminals available in work areas throughout the hospital. For example at Southmead Hospital, details of inpatient management information already recorded on the patient administration system are transferred to the medical diagnostic index producing a minimum data set comprising patient's name, age, address, name and address of the general practitioner, date of admission and discharge, coded reason for admission and diagnostic code (both using the specialty specific codes compatible with the International Classification of Diseases, 9th revision (ICD9), and the Office of Population Censuses and Surveys classification (OPCS4) derived for use in this hospital), drugs on discharge, details of follow up, and the name of the senior house officer producing the summary. This is linked to eight lines of free text producing an initial discharge summary providing nursing advice to health visitors and a pharmacy card for drugs to take home.

Direct input is possible from wards, outpatient departments, and casualty with terminals in the secretary's and other offices. Its use in other areas of patient care such as outpatients and casualty allows the identification of a child with a high risk of child abuse by highlighting certain diagnostic codes when a child is seen. In the future a patient activity database will allow cross referencing of information between hospital systems such as the medical data index, patient administration system, pharmacy, wards, biochemistry, chemical pathology, radiology, and subsequently between the hospital and community. Each summary takes approximately five minutes to generate and the data, its accuracy, and the completeness of data, are checked at weekly meetings. The Family Practitioner Committee was consulted before the setting up of this system and continue to give feedback about its usefulness. Confidentiality can be protected by entry codes appropriate to different levels of staff allowing users differing levels of accessibility to sensitive patient information.

(B) DIAGNOSTIC CODES

There are a number of diagnostic coding systems available such as ICD9 and OPCS4 and the Read classification[9] all of which are cross referenced. The Read coding system is likely to prove particularly helpful for paediatric inpatient and outpatient practice, although some considerable development of the system for specialty use is still needed. The BPA has produced three useful booklets containing paediatric and perinatal appropriate codes compatible with the ICD9 (1977) and similar attention to paediatric codes will be necessary after the imminent introduction of ICD10.[10] The diagnostic codes used in our minimum data set at Southmead are derived from these.

(C) DIAGNOSTIC RELATED GROUPS

The purpose of diagnostic related groups (DRGs) is to try to distinguish conditions with differing mean lengths of stay and resource expectations. DRGs were produced from a US national sample which specifically excluded children's hospitals so not surprisingly were of little use in paediatric practice. The problem for paediatrics is that mean lengths of stay are very similar for most diagnoses (table 1). More recently paediatric modified DRGs (PM-DRGs) have been developed which are more specific (in neonatology 46 PM-DRGs are proposed rather than seven). They make possible calculation of resource expectations in this specialty from different diagnostic groups.[11] As treatments and costs change with the introduction of new technologies the resource expectations will need continual revision.

Table 1 Top 15 diagnoses (Southmead Hospital)

Diagnosis (ICD9 code)	*% Of total admissions*	*Mean (SD) length of stay (days)*	*Mean age (years)*
Asthma (493)	11	1·50 (0·54)	4·2
Non-specific viral infection (079)	10	1·21 (1·52)	3·7
Ill defined intestinal infections (009)	9	1·38 (0·46)	3·3
Acute upper respiratory tract infection (465)	7	0·94 (0·54)	1·8
Non-specific abdominal pain (789·09)	6	0·86 (0·20)	11·1
Febrile convulsion (780·30)	4	0·98 (0·50)	2·1
Accidental ingestion (E858)	4	0·93 (0·61)	3·2
Healthy infant (V30)	4	0·93 (0·60)	0·4
Concussion (850)	4	0·79 (0·32)	7·5
Bronchiolitis (466·1)	3	2·10 (1·58)	0·6
Acute laryngotracheobronchitis (464·2)	2	1·20 (2·31)	1·9
Urinary tract infection (599)	2	1·80 (1·46)	3·4
Enteritis due to specified virus (008·6)	1	1·30 (1·30)	3·5
Acute tonsillitis (463)	1	1·40 (1·23)	5·3
Pneumonia, organism unspecified (486)	1	2·08 (1·69)	5·1

(D) SEVERITY CODING

In addition to the minimum data set a system of codings of severity is required before the comparison needed for criterion based audit (see mechanisms of audit) can be undertaken. There are a number available including the Read classification based on three dimensions; disease, disability, and pain.

Mechanisms of audit

Although computerised data collection systems such as the one described are at the heart of setting up audit they are not essential to the practice of medical audit in any department. Groups may meet once a week for an hour either at the beginning, middle, or end of the day or audit meetings may take the place of some postgraduate meetings.

If there are fewer than three consultant paediatricians in a department, then it will probably be necessary to arrange joint meetings with neighbouring health districts. Once barriers (if they exist) have been broken down, most departments would find review by outsiders valuable. Junior medical staff should be required to attend and for some topics other professionals such as nursing staff or therapists may be included. Joint meetings with general practitioners or other specialists and departments are likely to be fruitful.

The aim of the audit is to compare clinical care by seeing how clinical practice matches up to agreed practice. In a relatively subjective way this is already done in perinatal mortality meetings. 'Criterion based audit' offers a more objective process. Explicit and measurable criteria for good practice at unit level are agreed upon against which practice can be compared. The advantage of criterion based audit is that much of the initial screening could be done by non-medical staff, and the differences between hospitals can easily be identified as can improvements in performance measured over time within a particular unit.

Personal experience of paediatric medical audit

Recently both at Pinderfields and Southmead Hospitals formal minuted audit meetings lasting approximately one hour have been set up to which all members of the medical staff attend. At Pinderfields Hospital in the absence of a clinical information system these are largely based on case note reviews and, every three months or so the district information service produces data on length of stay for conditions such as head injury, febrile convulsion, or asthma to allow the effects of changes in policy to be reviewed. Written guidelines have been available in the unit for 10 years and are updated regularly.

At Southmead Hospital the first meeting of the month is taken up with analysis of data collection for the previous month, difficulties are discussed with a representative of the computer department who always attends this meeting. It is hoped that as teething problems are removed from the data collection system this meeting will be changed to every three months. A further meeting looks in detail at aspects of inpatient management. Specific cases identified by the consultants before the meeting from the week's discharge summaries are first discussed and then criterion based audit is used to look at randomly selected case notes of common admission diagnoses where guidelines have been agreed such as gastroenteritis, convulsions, and asthma (table 1). The third week involves a similar exercise looking at common outpatient clinical problems such as management of bed wetting or 'funny turns'. The fourth is generally used to look at interface areas with paediatrics and joint meetings are held with other medical staff to discuss specific topics—for example, with surgeons (pyloric stenosis), neurosurgeons (treatment of posthaemorrhagic hydrocephalus), radiologists (use of chest and skull radiographs), the casualty department (recognition of non-accidental injury), pathology laboratories (jejunal biopsy), and community services (immunisation and developmental screening).

It is an important principle that the meetings are seen to be audit of the work of the paediatric unit as a whole rather than one group (the consultants) assessing the performance of another (the senior house officers). To this end topics for discussion are chosen by the group and individuals are assigned to analyse and prepare data for presentation in turn. In any case many of the problems identified are due to administrative error rather than poor clinical judgment. An audit secretary records the minutes which are circulated to medical staff with a record of actions taken.

Simple analysis of the data is made every three months (total number of admissions, discharges, and completed discharge summaries) and a more detailed assessment yearly as part of the annual report. Any associations between the variables in the minimum data set can be analysed, table 2 shows the top 15 reasons for admission expressed as a percentage of total admissions and table 1 the top 15 diagnoses with average age and length of stay.

Table 2 Top 15 reasons for admission (Southmead Hospital)

Diagnosis	*% Of total admissions*
Wheeze	15
Acute abdominal pain	11
Infection	9
Vomiting	9
Convulsion	7
Ingestion of toxic substance	7
Fever	6
Cough:acute	6
Accident at home	6
Diarrhoea and vomiting	6
Routine for investigation	3
Stridor:acute	3
Headache	3
Diarrhoea	2
Crying	2

Audit of audit

Apart from its educational value it is hoped that medical audit will lead to a change in practice—for the better. It remains to be seen whether the time and effort spent in such activity truly improves patient care. Review of the time spent and review of measures of change for the better must be an integral part of the audit process.

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Useful booklets

South West Regional Hospital Medical Advisory Committee. *The regional approach of medical audit.* Bristol: South West Regional Health Authority, June 1989.

Shaw C. *Medical audit: a hospital handbook.* London: Kings Fund Centre, February 1989.

Useful addresses

Association for the Study of Medical Education, Level 10, Ninewells Hospital and Medical School, Dundee DD1 9SY.

Kings Fund Centre, 126 Albert Street, London NW1 7NF.

CBO National Organisation for Quality Assurance in Hospitals (Churchilllaan 11), PO Box 20064 3502 LB, Utrecht, The Netherlands.

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PERSONAL PRACTICE

Management of migraine

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Definition and diagnosis

Uncertainties about the definition of migraine and the absence of any 'test' or marker make its diagnosis difficult at any age. The difficulty is greater in children whose ability to recount previous or changing symptoms may be limited. Most importantly, children tend to present early in the course of headache disorders (because of parental anxiety) so that the reassurance of continued wellbeing in the face of a long history is unlikely.

Though diagnostic criteria are necessary for epidemiological study, they are unsatisfactory for clinical use, particularly in childhood, because for example, the visual phenomena of classical migraine are uncommon, and prostration, vomiting, and abdominal discomfort may overshadow the headache.[1 2]

In clinical practice it is simpler, and safer, to accept as migraine recurrent headaches which are *paroxysmal* (an essential characteristic), provided that there is return to full normal health—both mental and physical—between attacks, that development continues normally, and that other causes of headache have been excluded (indications for investigation are given below). This demands a period of observation to establish that normal health is indeed maintained between attacks. Diagnosis is thus by *exclusion*, and *longitudinal* observation.[1] A family history of migraine is not a reliable pointer to the diagnosis: the detail is often vague and the prevalence of migraine in the community is too high. The distinctions between common migraine (migraine without aura) and tension, and psychogenic, headaches may not be clear, and these disorders can coexist in children as well as adults. Their clinical management, however, overlaps.

There are probably no *essential* differences between migraine in childhood and that in adult life, though before puberty boys slightly outnumber girls. Basilar migraine is commoner in childhood, and other variants are probably also more often seen in childhood than in adults. It is also often stated that migraine equivalents are commoner in children.

'EQUIVALENTS' OF MIGRAINE

Although headache is an essential feature it is only one aspect of migraine and the neurological symptoms (including mental, motor, sensory, and autonomic disturbances) may be more prominent than the headache; rarely, they may occur without it—so called 'abortive migraine'. When abortive migraine consists of a scintillating scotoma in a subject who has classical migraine attacks at other times the episode can properly be accepted as an 'equivalent' of migraine. When the disturbance consists of necessarily ill defined autonomic (so called vegetative or visceral) symptoms, in a child who has no other complaints the situation is different. The symptoms *may* represent abortive migraine but the list of alternative diagnoses is long and full investigation is essential. And unless or until recurrent paroxysmal headaches occur, the symptoms should not be labelled as migraine. Modification of symptoms by antimigraine remedies does not favour the diagnosis of migraine because a placebo effect is common.[3]

Careful observation and inquiry may reveal that headache is a feature in some presentations initially thought of as migraine equivalents, and this typically becomes clearer as time passes. Prospective studies in children with recurrent abdominal pain syndromes do not show migraine as a common sequel.[4]

Indications for investigation

Migraine should be seen in the context of *unexplained headache*—that is, headache without symptoms or signs indicating a specific diagnosis. Whenever possible it needs to be distinguished from tension headache and headache of psychogenic origin, and from true conversion (hysterical) headache. Most importantly, migraine needs to be distinguished from headache caused by intracranial disease that has not yet been detected, either because examination has been inadequate or presentation has been too early in the course of an evolving disorder. The nature of a headache does not indicate its aetiology, for example, headache caused by a brain tumour may be throbbing or unilateral, or show long remission[5–7]—and children with migraine may wake during the night or (occasionally) vomit without first feeling nauseated.[8]

The features that are indications for further

Indications for further investigation

- New neurological symptoms or physical signs
- Failure to return to full normal health between attacks of headache
- Increase in the frequency or severity of headaches
- Headache not relieved by simple analgesics
- Any suggestion of change in personality, behaviour, or performance of any skill at home or at school—for example, moodiness, irritability, lethargy, loss of interest, or fall in academic performance
- Any suggestion of slowing of developmental progress, particularly in cognitive and motor skills
- Retarded physical growth
- Head circumference exceeding the 97th centile, or considerably out of line with height
- Young age (less than 6 years)

investigation (by imaging and other tests) are shown in the table.

The duration of observation that is desirable before one can be confident that recurrent headaches are not the result of raised intracranial pressure is discussed by Honig and Charney,[6] who noted that 60 of 72 children who presented with headaches caused by brain tumour were correctly diagnosed within four months of the onset of symptoms, and that of the remaining 12 children, 11 had symptoms or signs that *should but did not* lead to earlier diagnosis. These included small stature, polydipsia, alteration in character or frequency of headache, behavioural changes, visual features, and incoordination of movement. Flores *et al* noted worrying delays in the diagnosis of brain tumour in childhood, finding histories of longer than 26 weeks in 21 of 79 children.[9]

In general a child who develops unexplained headaches should be watched carefully for at least six months from its onset, and should be occasionally reviewed thereafter. It is clearly undesirable for children to visit a hospital clinic repeatedly and surveillance 'in passing' by the general practitioner and the community health service is more appropriate. Follow up should include attention to school progress (both social and academic) and to physical activities, and should include perusal of school reports.

REASON FOR PRESENTATION

The first step in treatment of migraine is to discover the reason for presentation: why has the child been brought at this particular point? The problem may be one of frequent worsening attacks, but equally may be of failure at school (primary or secondary), or parental anxiety (not always justified), and in these circumstances prescription of drugs may well increase the problem. Often parents just want reassurrance that they are managing the problem correctly; sometimes they come only to inquire about some widely advertised new drug, or they have heard of an aquaintance with a brain tumour. Medicinal treatment is indicated only if the reason for consultation lies in the child.

PROVOKING FACTORS

Many children with migraine also have tension headaches, and sometimes in addition psychogenic headaches masking school refusal. The prominence of these aspects will indicate whether psychiatric referral is indicated.

Provoking factors are often closely interrelated. They include stress, fasting, food factors, fatigue, light, and minor head trauma (including football).[10] Most are inconsistent in their effects, so that while sometimes active they are at other times harmless. Parents may lack information about bullying in school or may withhold information about neglect and abuse. A single consultation is rarely enough in children: parents often need guidance about what to look for before an adequate history is obtained, and in most cases a school report is necessary. A lot of attention is given to dietary factors in migraine,[11] but the prevalence of dietary migraine is uncertain and there are important reservations about the use of elimination or exclusion diets in childhood on grounds of health,[12] compliance, and cost.[13] A controlled study in children showed equal benefit from, and no differences between, a diet high in fibre and the same diet excluding vasoactive amines.[14] Some 'alternative treatments' are aimed at reducing stress, which is a well recognised provoking factor in all benign recurrent headache disorders in children. There is no evidence that sophisticated manoeuvres such as acupuncture and biofeedback are superior to the 'ordinary' psychotherapy implicit in the process of diagnosis, explanation, and reassurance.[15]

Treatment

Wherever possible non-medicinal treatment should be used, aimed at altering the child's circumstances. Treatment may include removal of such distant causes as batswing ears (leading to bullying, failure at school, and frequent migraine) or tonsillectomy (relieving sleep apnoea, daytime fatigue, school failure, and increasing migraine with or without tension headache). There is no value in specific headache medication in children with psychogenic symptoms.

TREATMENT OF THE ACUTE ATTACK

Medication should be given at the first symptom of an impending attack. For children of school age it should be easily available in school so that the child may avoid being sent home, instead being encouraged to return to class after a brief rest.

Initial drug treatment should offer a means of pain relief: once this has been experienced much anxiety (and therefore risk of further attacks) is reduced. Analgesic treatment should be given early in sufficient dose in absorbable form. Soluble paracetamol or aspirin (the use of which is limited in the United Kingdom), sometimes with metoclopramide (of unproved benefit and with a high risk of dystonic reactions in children[16]) usually give relief especially if followed by a brief rest in a darkened room.

When migraine attacks are severe and simple remedies have failed then codeine may be tried, and parenteral diazepam or chlorpromazine can be used if the child is distressed. Use of these drugs must be cautious, and over medication is common. Ergotamine preparations can be used in children, with the usual cautions about dose and frequency of administration. There is reluctance to prescribe ergotamine for children under the age of 10 years, but its use is justified in severe presentations. When vomiting heralds an attack of migraine then sublingual, intramuscular, or rectal administration will be necessary. Propranolol is beneficial in treatment of acute attacks in adults, but has not been used in this way in children.[17] A controlled study of the calcium channel blocker nifedipine in treatment of acute attacks in adults showed no beneficial effect.[18]

INTERVAL TREATMENT

Most children with migraine (and their parents) find that effective pain relief for each headache as it occurs is adequate treatment. For the few in whom relief cannot be found or who continue to experience frequent attacks, then interval drug treatments must be tried. There is no proved effective prophylactic against migraine in children. Despite early favourable reports recent controlled studies of propranolol, timolol maleate, clonidine, and pizotifen all failed to show any superiority over placebo.[19] A controlled trial of dihydroergotamine as a prophylactic in children showed no benefit.[20] There are promising reports of the effects of flunarizine,[21] and other calcium channel blockers, and side effects observed in adults[22] have not been seen in children.[21] A controlled trial of L 5-hydroxytryptophan in children with migraine gave negative results,[23] but there is interest in the development of new 5-hydroxytryptophan agonist drugs, which have not yet been tried in children. With increasing understanding of the adverse effects of antiepileptic drugs on cognition there is no longer a place for their use in headache disorders, except in the rare cases of true seizure headaches.[24] Disability from migraine is rare, but it can be considerable with severe effects on schooling and behaviour, and there remains great need for effective prophylaxis.

Conclusion

Most children with benign headaches, whether migraine or tension headaches, respond within a few months to reassurance, general advice, and simple remedies for attacks as they arise. Because most children do improve, or show natural remission, failure to respond should be regarded as an indication to reconsider the diagnosis.

Until migraine can be identified by some investigation or marker it should remain within the area of headache problems in general, with diagnosis by exclusion of other causes.

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PERSONAL VIEW

Selective medical examinations for school entrants: the way forward

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Routine medical inspections have been a traditional part of starting school in the United Kingdom since the early 1900s. When the school health services were incorporated into the NHS in 1974 medical inspections ceased to be a statutory requirement, and the numbers of routine medical examinations of children over the age of 5 have declined. Most areas have, however, retained a system of routine medical examinations for all children when they start primary school, sometimes including a thorough neurodevelopmental assessment as well as a physical examination.[1 2]

The value of this system was questioned by the Court Committee on Child Health Services,[3] and in later reports.[4 5] Retrospective analyses of school entry medical examinations have not shown routine examination of all children to be particularly advantageous[6–9] and, increasingly, the value of such routine examinations is being challenged.[9 10] Systems of selective medical examination at the time of entry to primary school are already successfully in operation in some parts of Britain and Australia.[11–13]

This paper describes the organisation of selective school entrance medical examinations in a socially deprived inner city district of London with a mobile population, and presents the results of the initial pilot study that assessed the feasibility of such a system.

Background

The former health district of Paddington and North Kensington constitutes a deprived inner city area of London, with widespread unemployment and a large proportion of recent immigrants especially from Morocco and Bangladesh. Services for preschool children are based at local child health clinics, and include immunisation and developmental screening. The latter is performed by community child health doctors at 6 weeks, and by health visitors at 15 months and 3 years. When a child starts school at the age of 5 years, the community child health record is transferred from the health visitor to the appropriate school nurse, either directly or through the centralised school health department. Before the start of the selective medical system, every child was seen by both the school nurse (for testing of hearing and vision and measurement of height and weight, and completion of a health questionnaire with the parent) and the school doctor (for detailed medical and neurodevelopmental examination) after one term in school.

Selection for medical examinations

A system has been introduced whereby the subgroup of children who actually need a medical examination is identified and the remaining children are seen by the school nurse for a health interview. The selection is carried out jointly by the school nurse and doctor, who review the preschool records and have discussions with parents and teachers.

At the end of each term, children who have started school that term are reviewed. The preschool community health records are studied, particular attention being paid to concerns expressed at the child's 3 year check. The immunisation record is noted, and whether a record has been made of testicular descent and auscultation of the heart. A meeting is held with the reception class teachers at which they are invited to voice any concerns they have about that term's entrants. The meeting is also used as an information sharing exercise, enabling the teachers' concerns to be discussed in the light of the child's health records, and allowing information to be passed to the teachers about any major health problems of which they have been unaware.

As a result of this review process, a number of children can be identified as needing a medical examination. Children with chronic health problems, those previously identified as having possible special educational needs (for example, defects of vision or hearing, or developmental delay), and those with a history of child abuse or severe emotional or social deprivation, come into this category, as do children about whom the teachers are worried. Not all such children automatically see the doctor, however. The particular problem is discussed by the doctor and nurse; occasionally more information has to be obtained, such as hospital letters. A medical examination is then arranged if the problem seems to need a doctor to clarify matters or to intervene. In some cases—for example, a child with asthma who is not having difficulties at school—a medical examination is not considered appropriate.

Initially a medical examination was also arranged if preschool records were not available or if a child had no record of a 3 year review and had not been seen subsequently by a doctor or health visitor. This system was modified after one term of the pilot study to exclude children who were presumed to have had preschool health care but whose records had not yet been received by the school nurse; children new to the United Kingdom are still seen by the school doctor.

The remaining children are all seen (with a parent) by the school nurse for a health interview. The existing questionnaire is used to obtain details of past medical and developmental history, present symptoms, and immunisations; this is either sent to the home for the parent to complete before the health interview or completed by the school nurse and the parent together. Parents are asked directly about any concerns they may have about their child, and are asked whether they wish to see the school doctor. The child's height and weight are recorded and hearing and vision are tested.

The health interviews and selected medical examinations take place in the child's second term at school. Those having medical examinations have their growth, hearing, and vision checked by the school nurse in the usual way, and the same questionnaire is used as for the health interview. A few children are offered a medical examination after their health interviews, either at the parent's request or if the school nurse identifies a problem that cannot be dealt with simply by discussion with the school doctor. If immunisations are incomplete parents are invited to bring the child to the next immunisation session at the local child health clinic.

Administration and follow up

Details are recorded of the number of health interviews and medical examinations carried out, the problems that have been identified, and the action to be taken. At the end of each term a review is made by the school doctor and nurse of the term's medical examinations and health interviews. This is to keep track of non-attenders, and a check that all planned interviews and medical examinations have taken place. A check is also made of outstanding immunisations to ensure that the child has been taken to the clinic if necessary.

Subsequent review and monitoring of problems or defects can mostly be carried out by the school nurse, who will have received appropriate training. These include the management of enuresis, or monitoring of minor abnormalities of vision.

Results of pilot study

Two schools in North Kensington were included in the pilot study, both representative of the district as a whole. A total of 52 children aged 5 started school during the year being studied. Initially 14 (27%) were selected to have medical examinations; the rest saw the school nurse for a health interview. After the health interview, a further three children (6%) saw the doctor. The reasons for the medical examinations and their outcomes are shown in table 1. The most common reason for an examination (accounting for 35% of the total) was the absence of preschool records. The only problems identified in these children were one hearing deficit and one minor defect of visual acuity; in both cases the problem was identified by the school nurse on screening. Four children (24%) were seen because they were on the Child Protection Register; for all these follow up by the school nurse was felt to be appropriate. Two (12%) were seen because of teachers' concerns and two at the parents' request.

Health problems identified

The main problems identified at both the health interviews and the medical examinations are shown in table 2. Altogether, 20 children (38%) had a total of 24 health problems. Five of these problems were already known to the community child health services; a further two were receiving treatment but were not recorded in the community notes. Another four children's parents (8%) were worried about their children's health; two of these children subsequently saw the doctor and all were reassured with no further action being required. Defects of hearing and vision were the most common, accounting for a total of 11 of 18 problems (61%). None of these defects had been pre-

Table 1 Details of selective medical examinations

Reason for medical examination	*No (%)*	*Findings*	*Action/follow up*
Initially:			
New immigrants	3 (18)	All healthy	None
Missing records	3 (18)	Hearing loss (n=1)	Referred for audiological assessment
		Visual acuity deficit (n=1)	School nurse to follow up
		Healthy (n=1)	None
History of congenital dislocation of hips	1 (6)	No disability	None
Asthma: for evaluation	1 (6)	Well controlled	None
On Child Protection Register	4 (24)	All healthy	School nurse to follow up
Teacher concerned:			
Abdominal pains	1 (6)	Resolved before medical	None
Developmental delay	1 (6)	Marked delay	Referred to child development centre
After health interview:			
Parental request:			
Sleeping problem	1 (6)	Emotional upset	School doctor to follow up
'Blocked nose'	1 (6)	Normal adenoids	Discussion and reassurance
School nurse request:			
Hearing problem	1 (6)	Mild hearing loss	School nurse to follow up
Total	17 (100)		(n=2) Specialist referral (n=3) School nurse to follow up (n=1) School doctor follow up

Table 2 *Details of all health problems identified*

Problem	Newly indentified	Not known to community health services but receiving treatment	Known to community health services	Total
Hearing	7	0	0	7
Vision	6	0	0	6
Speech	0	1	0	1
Enuresis	2	0	0	2
Urinary tract infections	0	1	0	1
Asthma	0	0	1	1
Sleeping problems	1	0	0	1
Developmental delay	1	0	0	1
Adverse social circumstances	0	0	4	4
Total	17	2	5	24

viously recognised; two of the children (representing three problems) needed referral for specialist assessment. We were encouraged by the fact that our rate of detecting problems was similar to that in districts in which all 5 year olds are routinely examined; the problems were also similar.[9 14] This suggests that the selection criteria are adequate and that it is not necessary for a child to see a doctor for relevant health problems to be detected.

Non-attenders

We decided that if parents did not attend for health interview a home visit would be made by the school nurse to complete the questionnaire and to obtain consent to test the child's hearing and vision at school. Eleven of the 52 children had not attended for health interviews by the end of the school year but were successfully seen at the beginning of the next term and no home visits were necessary. The secretary of one school was, however, invaluable in reminding persistent non-attenders of their appointments, and home visits might well have been needed without this help. Non-attenders for immunisation were reminded once by the school nurse; as a last resort immunisations could be undertaken by the doctor or nurse at school, and three children from this cohort were eventually immunised at school.

Audit

To check that the selective medical examination system identified problems correctly, all children will be reviewed at the age of 7, by means of a questionnaire (already in use for the junior school reviews), which will be completed by the parents.

Problems in implementing the new system

Problems were experienced in three main areas. The first, and most troublesome, was that of missing preschool records. We had anticipated this as North Kensington has a rapid turnover of children from mobile families with a high incidence of health problems and we initially questioned whether selection would be worth the extra administrative effort if most children would need to be seen to confirm that all was well. In practice, although problems were encountered in obtaining the preschool records, these did not upset the system. It was not only the mobile families who had this problem: several children known to have attended one of the two local child health clinics for 3 year checks and preschool booster immunisations were without records on school entry. This resulted in excessive administrative work for the nurses in trying to obtain records before deciding whether the child needed a medical examination, and in arranging unnecessary medical examinations.

Our eventual policy of offering routine medicals only to those children who definitely did not have records (predominantly new immigrants) was validated by the results: parents could usually confirm that their child had received preschool surveillance, and could supply the relevant information. Missing records and mobile families are a feature of inner London districts; a need for improved transfer of information has been suggested.[14] Records held by parents would help and we hope that improved liaison between the school health teams and general practitioners will soon obviate the need for medical examinations for which the only indication is ausculation of a child's heart or confirmation that the testes have descended.

The second problem was the reservations that the educational staff had about the new system. These were encountered in both schools, but for different reasons. One head teacher felt that the responsibility for identifying children with problems was being shifted too heavily on to the teachers, and was unhappy about spending time meeting with the school nurse and doctor each term; this meeting was, however, preferred to our alternative suggestion of a questionnaire being completed by the teachers for each child. By the end of the pilot year, these worries seemed to have abated and the system was working well. In the other school, the problem was the opposite: a head teacher who had always worked closely with the school health team found it hard to accept that some worries that she raised could be dealt with competently by the school nurse without the need for a full medical examination. This, too, was only a temporary problem.

Finally, the school nurses found their changed role, with more responsibility for advising parents directly, somewhat daunting at first. The solution was to encourage regular discussions between the school nurse and doctor, which allowed joint decisions to be made and provided the necessary support for the nurse.

By the end of the pilot year the nurses were enthusiastic about the selective system and found their new role more effective and more satisfying than in the past.

Discussion

At school entry the school health team aims to ensure that there are no unrecognised health problems that may restrict a child's ability to benefit from education. Most problems identified concerned vision and hearing,[9 14] both of which are best detected by screening.[5] Physical conditions may account for about 20% of recorded problems[9]; educationally relevant conditions are unlikely to be detected by physical examination alone in the absence of a history of chronic illness or past developmental, behavioural, or psychosocial problems.[13] The proponents of routine school entry medical examinations for all children are largely concerned about detecting 'clumsy' children or those with possible learning difficulties.[1 2 15] There is no doubt that existing detailed neurodevelopmental screening examinations are predictive of later problems if they are appreciably abnormal,[2 16] although they have been criticised for (among other things) lack of standardisation.[17] The management of these problems, however, requires a multidisciplinary approach and it can be argued that the classroom is a more appropriate place to identify children who are underfunctioning. If necessary, health service time might be better used to increase teachers' awareness of predictive signs. In our pilot study the only child with a previously unrecognised neurodevelopmental problem was identified by the class teacher.

Another argument in favour of routine medical examinations is that not all children have access to preschool health care.[1] The areas in which selective medical examinations are already used are mostly rural with good uptake of preschool surveillance,[12 13] but at least one inner city system has been reported,[11] and our results show that even in a severely underprivileged area a policy of selective medical examinations can work well. Inadequate preschool surveillance should not be replaced by extra screening at school but by improving preschool services, now recognised as the most important aspect of child health surveillance.[3 5]

It has been said that parents like school medical examinations.[1 18] No parents in our pilot study objected to the selective system and many were appreciative of their increased opportunity to discuss worries with the school nurse. Only two of the 38 parents seen (5%) asked for medical examinations, both for valid reasons. We have deliberately opted for a system of health interviews with personal contact between parent and school nurse, rather than a postal questionnaire with screening of growth, hearing, and vision in the absence of the parent. This seems to have contributed to the parents' acceptability of the system. In line with current trends some responsibility was placed on the parents to express their worries and to request to see the school doctor. The traditional school health system leaves many parents confused and uncertain about the way it operates,[19] and to be effective, the school health team of the future will need to provide advice for parents about the selective medical system and how to use it. If parents are to be able to play their full part it will be especially important for them to know the names of the school doctor and nurse and how they can be contacted and to be kept informed of the outcome of surveillance that their children receive.

The many positive aspects of selective medical examinations have been emphasised by our study. The role of the school nurse has been redefined, emphasising her position as the key person in the school health team. The school doctor can then be used more appropriately to provide secondary care. This leads to increased job satisfaction for both nurse and doctor. Children with disabilities, those with emotional problems, and those from deprived backgrounds, benefit the most from school health service time, but this is not always available and it has been pointed out that the redistribution of resources resulting from a system of selective medical examinations should lead to more medical time being available for those who really need it.[10] We found that a problem could be dealt with thoroughly in a relatively long initial consultation, sometimes avoiding the necessity for repeat attendances or for referral elsewhere.

It now seems that there is no longer a place for routine medical examinations for all children at school entry. A health interview with the school nurse maintains the direct contact that parents prefer and allows efficient screening. Those children who do have problems benefit from the extra medical time available to them. There is an increased opportunity for health education by the school nurse. Some of the medical time freed may be profitably used in developing training programmes to increase the awareness of teachers of common health problems in school age children, which is less than optimal both for neurodevelopmental problems[15] and conditions such as asthma.[20]

Child health surveillance is currently the subject of much interest, and attempts are being made to rationalise the services provided. The emphasis for the future is on increasing parental concern with and responsibility for their children's health,[5] with a reduction in less productive routine screening procedures. Selective school medical examinations, which are an important part of this new approach, can be successfully introduced in even a severely disadvantaged area with clear benefits to all.

We thank Mrs B Phellas and Mrs R Peltier for piloting the health interviews, Miss S Nason for help with data analysis, and Miss J Rifai for typing the manuscript.

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Circumcision again

The fate of the foreskin has not been to the fore as a topic of paediatric conversation in Britain since Douglas Gairdner wrote his memorable paper.[1] Nevertheless, the pros and cons of routine circumcision of newborn babies are keenly debated in the United States and the *New England Journal of Medicine* recently published two opposing views.[2] [3]

Among arguments in favour of neonatal circumcision are the avoidance of balanoposthitis and phimosis and an apparent decrease in the incidence of infantile urinary infection and of later cancer of the penis in circumcised males and of cervical cancer in their sexual partners. Dr Schoen believes that the benefits of circumcision far exceed the risks but Dr Poland casts doubt on the methodology of the studies on urinary infection and recommends avoidance of human papilloma virus infection by reducing the number of sexual contacts and by appropriate use of condoms as more effective ways of preventing penile and cervical cancers. He concludes that the benefits of routine circumcision are uncertain and the decision should be left to the parents.

My guess is that British paediatricians will await further evidence before recommending routine operation for normal newborns. As for myself, I'm prejudiced. The possibility that such a primitive ritual could have any scientific justification is one I find difficult to swallow. How did nature, God, evolution, whatever you want to call it, get it wrong? Or did it?

ARCHIVIST

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SISTER JOURNALS—EUROPE

European Journal of Pediatrics

This is a well recognised journal which is now in its 149th volume and is produced by Springer International. The texts are in English and are well presented with good reproduction of graphs and photographs.

The content is widely varied covering most fields of paediatrics. Some are informative and impart to the reader information which may be useful in clinical practice. Unfortunately there is a considerable amount of 'paediatric philately' which would be best reported in other subspecialist journals or as short reports in this one.

It would appear possible that the journal suffers from the fact that it would not be the first choice for most authors. Most Europeans including the British would seek to publish their information in their own national journals rather than in others for their own chauvinist reasons. The effect is there is little in the European journal which is new or revelatory.

The acid test of any publication is whether one would buy it. I feel this journal passes this test if for no other reason than with the approach of 1992 it is important that there is a increase in the interchange of ideas and scientific truths across national borders. In this regard it is interesting to see that in the references most authors have cited other international workers and not just those of their own nation. I feel this journal could be improved if those of us who write regularly would seek to publish in these pages to the advantage of both ourselves and our fellow Europeans.

G McCLURE

Forty years ago

Acrodynia ('pink disease')

Acrodynia is a chronic condition affecting mainly infants from the age of 6 months to 2 years. The clinical picture is one of persistent misery and apathy. The child takes no interest in his surroundings and resents being handled, even by his mother. He has photophobia and buries his head in the pillows. There is appreciable tachycardia, the limbs are hypotonic, and the hands and feet are painful, red, and swollen. There is excessive sweating and generalised erythema (hence the descriptive term 'pink disease') with peeling of the skin.

Over a period of six years from 1943 to 1949 Leys collected a personal series of 30 cases of acrodynia which he reported in a review of the literature.[1] The first case in this country had been reported in 1923. Although the mortality of acrodynia was low and there were no deaths in Ley's series, nevertheless in England and Wales there were 20 deaths from the disease in 1926, 88 in 1936, and 103 in 1947.

Leys discussed the possible causes of acrodynia. Recorded necropsy findings showed only nonspecific degenerative changes of the central nervous system, peripheral neuritis, and the effects of secondary infection. He rejected previously mooted causes, such as vitamin B deficiency and allergy but noted that there were some clinical similarities with dermatomyositis and scleroderma in adults; he had reservations about mercury poisoning. He concluded that the aetiology of acrodynia was still unknown and suggested that it was a hypothalamic disturbance that might possibly be due to a primary emotional disorder.

Chronic mercury poisoning or hypersensitivity to mercury had recently been put forward (and is now accepted) as the cause of acrodynia because of the resemblance to classical mercury poisoning and because of the frequent finding of excessive amounts of mercury in the urine of affected infants. At that time mercury was commonly administered to infants in teething powders and vermifuges or in ointments for various skin conditions; 52 of 100 mothers questioned by child health staff in Kent had given their children mercury containing powders, often weekly over long periods.

Childhood morbidity 1947–9

In the late 1940s Hackney Hospital, a general hospital in East London, had 700 beds. In the two years from 1947 to 1949 this hospital admitted 3159 children under the age of 15 years: one sixth of the total admissions.[2] The proportions of admissions in the various paediatric age groups were: under 1 year—12%, 1 to 5 years—38%, 6 to 10 years—31%, 10 to 15 years—19%.

About half the admissions were for infective or inflammatory conditions but the commonest single reason for admission was removal of tonsils and/or adenoids (22%). Admissions for upper and lower respiratory tract infections were respectively 15% and 10% of the total. All forms of trauma accounted for 11% and acute appendicitis for 4·5% of the admissions. There were 117 cases (3·5%) of abdominal pain in 31 of which a normal appendix had been removed. Of the 55 cases with the diagnosis of 'rheumatism', 42 had acute rheumatic fever and eight rheumatic chorea. The 25 cases of tuberculosis included two with meningitis and one with miliary. Infectious diseases accounted for 80 admissions and these included six cases of diphtheria, two of typhoid fever, and two of poliomyelitis. There were 21 cases of acute osteomyelitis, 15 of meningitis, two of pyloric stenosis, and a number of single cases of rare diseases.

Non-accidental injury was not a recognised diagnosis at the time. However, some 40% of the admissions for fractures of the skull and of those for fractures of the humerus were in children from birth to 5 years of age. For all other fractures the proportion in this age group was below 25%. Furthermore there were three fractures of the humerus and one of the clavicle in babies under 1 year of age.

There were 46 deaths in the two years. Fourteen of these (30%) were cases of pneumonia in infants under the age of 1 year. The remainder of the deaths were due to a wide variety of conditions including congenital heart disease, meningitis, rheumatic fever, and one death from congenital syphilis.

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Archives of Disease in Childhood 1990;65:1183

LETTERS TO THE EDITOR

Growth hormone deficiency in children with chromosomal abnormalities

SIR,—I read with some surprise the letter by Schwartz and Duck on the treatment with growth hormone of two children with chromosome deletions associated with multiple malformations, microcephaly, and mental handicap.[1] Though I too am intrigued that a cause of poor growth in some children with chromosome disorders might be mediated through a lack of growth hormone (although I cannot understand why they used growth hormone in their second case, as there was a very adequate maximum growth hormone response to insulin provoked hypoglycaemia (21·4 mIU/l)), this has surely to be tempered with a sense of proportion. Is it really appropriate clinical practice to use growth hormone in children with such major multiple physical and neurodevelopmental handicaps?

This example highlights for me what is becoming an increasingly worrying dilemma concerning growth hormone treatment. If, to children with true growth hormone deficiency, we add girls with Turner's syndrome, children who fail to grow as a consequence of intracranial irradiation for treatment of malignant disorders, children with other chronic diseases such as chronic renal failure, and now children with chromosome disorders and dysmorphisms, the queue for growth hormone treatment, an extremely costly item, becomes a long one. This is even without 'normal' short children whose treatment with growth hormone is surely an option we should now very seriously question.

Against a background of increasing financial constraints within health authorities the euphoria following the ready availability of biosynthetic preparations of growth hormone in 1985 will need to be better disciplined. Because growth in the short term can be accelerated after administration of growth hormone, and because there might also result an increase in predicted height of a few centimetres, does not mean it has to be used; this is an assumption that seems to be insidiously becoming part of paediatric practice.

More needs to be learned, beyond simple anecdotal experience, of possible detrimental effects to psychological wellbeing of shortness, which is often the major criterion for considering treatment. We also need to look in more detail at psychological outcomes of treatment. The problem of shortness is often as much a family concern as it is one belonging to the child, and parents' attitudes have to be better understood, as herein so often lies the source of the problem. At the same time we need to do as much as we can to help some children and their parents understand and cope with one of the apparent unfairnesses of life, as short stature is now so often viewed in our society, and not raise the false spectre of 'a pill for every ill'. The reality that sometimes some degree of a shorter than perceived ideal stature might be unavoidable may simply have to be accepted.

In the case of growth hormone treatment, it is difficult to avoid the conclusion that eventually there will need to emerge priorities in its prescription, which whether we like it or not, are likely to be determined in the end as much by monetary considerations as clinical need.

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Early identification of hearing loss: screening and surveillance methods

SIR,—Scanlon and Bamford have recently emphasised the poor sensitivity of the distraction hearing test as a screening procedure for the detection of childhood deafness.[1] A retrospective study conducted by us in Warrington revealed similar limitations of the distraction test. Of 41 children with severe, sensorineural deafness only 12 cases were detected at a mean age of 11 months as a result of failing the distraction test. Sixteen babies passed the test but were later found to be a deaf at the considerably later age of 41 months. This indicates that if screening procedures in the case of these latter children were unsatisfactory, a false negative group could have been inadvertently created where misplaced parental confidence contributed to delayed diagnosis. Most cases in our series were diagnosed as a result of referral after parental concern.

Even if the sensitivity of the distraction test was 100%, 8 months of age is far too late to make the initial diagnosis of nerve deafness as, by the time appropriate referrals are subsequently made after failing the test, several months may elapse before hearing aids are fitted.

The test itself is technically difficult to perform and the subtleties of result interpretation are often underestimated. It is difficult to maintain standards when large numbers of children need to be screened.

The conditions under which the test is performed are often unsatisfactory and sound proofing of all clinic premises would be prohibitively expensive.

Is it ethical to continue with a screening procedure knowing that at best it has poor sensitivity and that at worst it can actually be harmful by contributing to a delay in diagnosis? Alternative methods of diagnosis are currently being evaluated in West Berkshire. We await their results with great interest.

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Purchasers, providers, and community paediatricians

SIR,—Dr Appleyard's analysis of the problems awaiting children's services raises a further question.[1]

The process of contracting is described by the Department of Health as a dialogue in which 'all participants should be clearly identified as being either purchasers or providers'.[2] Dr Appleyard argues that logically this implies that consultants working in provider units will not be allowed to give advice to the purchasers of their services. This represents a considerable challenge to community paediatricians, who have a dual role.

The community paediatrician is a provider of services, for example, for children with special needs. But equally, he or she has important purchaser functions, in terms of local management, and information gathering. For example, immunisation and preschool surveillance are increasingly devolved to general practitioners, while the community paediatrician retains responsibility for the system centrally.

Information is power in the new health service, and it is central to the work of community paediatricians to be able to advocate the health needs of their child populations.

Division of this role would destroy the contribution of the community paediatrician to an integrated child health service. Unfortunately this may be an inevitable consequence of the NHS Review, which aims to provide services according to consumer choice rather than population needs.

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Is late walking a marker of congenital displacement of the hip?

SIR,—Johnson and colleagues record that 10% of 4275 infants born in 1984–5 and studied in Oxford health region had not walked by 18 months of age.[1] They point out that this figure is considerably in excess of that of 3–5% cited by studies in the 1950s[2] and 1960s.[3] The average gestational age of their late walkers at birth was 36·2 weeks. Not surprisingly, 46% of infants born before 28 weeks fell into this group, for no correction was made for preterm delivery. I find it hard to accept their argument that it is appropriate to ignore the 'lost' prenatal months, even though very preterm infants may have an associated impairment. Apart from the interpretation of the medical assessment, judging a preterm infant against a developmental scale designed for term infants is likely to create anxiety among parents whose child is slow to attain his or her milestones.

In the Oxford study five (1·2%) of the late walkers had orthopaedic problems. It would be of interest to know whether any of these children had congenital dislocation of the hip (CDH). Of course this diagnosis is now usually made long before an infant walks. This was not so 30 years ago, however, when I made a small study of 65 children born in Birmingham in whom the diagnosis was made after walking had commenced. The mean age of starting to walk in this group was 16·5 months (range: 11–28 months) as compared with 13·7 months for the whole population.[2 3]

Twenty two percent of these children with CDH were still not walking at the age of 18 months. Thus the commonly taught axiom that CDH does not delay the onset of walking is incorrect. Indeed, in a later study that I made in 1962, into the way in which the diagnosis came to be made in 244 cases of CDH (average age 19 months), 'late walking' was the fourth most common form of presentation (11%), after 'abnormal gait' (53%), 'short leg' (29%), and 'associated deformity' (21%).[4] No correction was made for gestational age but then CDH is uncommon among preterm infants.[4 5] In conclusion, while the ate diagnosis of CDH is becoming less common, the failure of a term infant to walk at 18 months remains a useful marker for this condition.

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Drs Johnson, Goddard, and Ashurst comment: While acknowledging Dr Dunn's point that some degree of delay in achieving motor milestones is to be expected among very preterm nfants, the high rate of impairment among the late walkers in this group means that immaturity' should not be too readily accepted as the sole reason for late walking. As so often in clinical practice, a balance needs to be achieved between causing unnecessary anxiety to parents and yet remaining aware of the risk of associated impairment in all late walkers, particularly those who were born very preterm.

There was just one infant among the late walkers who had associated congenital dislocaion of the hip. This had been detected, however, before the age of 18 months.

Lichen sclerosis

Sɪʀ,—As a paediatrician who has encountered eight new cases of lichen sclerosis in young children over a period of 18 months, I would like to add my observations to those of Drs Priestley and Bleehan and Dr Harrington.[1 2]

The earliest of these cases was a girl aged 6 years, who presented with dysuria and bleeding after a visit to a male neighbour—a regular babysitter. The girl gave a clear account of repeated sexual abuse involving frictional interlabial trauma. The neighbour admitted to these offences as well as to those on other children has since served a prison sentence. The findings were of gross lichen sclerosis with pallor, friability, and haemorrhage, with the hymen showing partial disruption at one site.

Of the other seven cases seen, a further two were associated with clear histories of sexual abuse. In another child, extensive hymenal damage was associated with behavioural and family factors, and abuse remains a worrying possibility.

Lichen sclerosis has therefore been noted by me in three children where sexual abuse was described, as well as in children presented by protective agencies, because of this and other behavioural symptomatology.

The suggestion that the presence of lichen sclerosis in someway excludes sexual abuse must be unacceptable. Indeed, if I were to use the statistical reasoning of Dr Berth Jones *et al* in terms of my own limited experience,[3] the presence of these changes would be linked to a sexual abuse diathesis in such significant numbers (50%), as to turn this argument on its head with equal frailness.

If lichen sclerosis is the outcome of chronic trauma in some children, then it must follow that every case requires careful study. Perhaps we should also be considering the possibility that these changes may relate to a local immune response to the recurrent presence of substances like semen, or contraceptive lubricant, both in adults and children.

My personal approach is to accept lichen sclerosis in children as a spontaneous unexplained phenomenon. I would not accept hymenal disruption, sexualised behaviour, or a child's disclosure as part of this phenomenon. The presence of lichen sclerosis in these circumstances can neither be considered 'spontaneous' nor 'unexplained'.

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Surveillance for anaemia: risk factors in pattern of milk intake

Sɪʀ,—We were interested to read Mills' study from east London, of the prevalence of anaemia in early infancy,[1] and fully agree with his conclusion that iron status is closely related to the type of milk consumed.

Prompted by a high reported incidence of iron deficiency in China, and concern in Hong Kong that babies were having a poor iron intake during weaning, in the mid 1980s we investigated the iron status of a sample of full term healthy Hong Kong Chinese babies. These babies were being followed up to monitor their growth and nutritional state and most were formula fed. Of our initial cohort of 174 babies only 8, 4, and 2% were breast fed at 2, 4, and 6 months respectively.[2]

Mean (SD) daily iron intakes at 6, 12 and 18 months were 8(5), 9(3), and 8(3) mg respectively, comfortably within the WHO dietary allowance of 5–10 mg. The mean (SD) haemoglobin concentration in 123 babies, at 18 months was 124 (8·9) g/l. Eleven had a haemoglobin concentration <110 g/l. Of these, seven had β thalassaemia trait, two showed a satisfactory response to iron treatment (2 mg/kg/day) for three months, one had an unchanged haemoglobin, and one defaulted further follow up. Three of 112 babies with haemoglobin of >110 g/l had a mean corpuscular volume <70 fl. Mean (SD) serum ferritin concentration at 18 months in 128 infants was 155·9 (24·8) μg/l, with only one having a concentration <7 μg/l.

We attributed this very low (~2% excluding β thalassaemia trait) incidence of iron deficiency to infant feeding practices, which provide: (i) an adequate iron intake during the weaning period from fortified milk formulas, iron fortified cereals, meat, and fish and (ii) a negligible consumption of pasteurised cows' milk with its low iron content and risks of causing occult intestinal blood loss.

These practices contrast with those described in Mills' study,[1] where, with an incidence of anaemia of 22%, continued breast feeding, with the early giving of pasteurised milk, were risk factors for anaemia. But the value of prolonged formula feeding, with iron fortified milks that comply with international standards, as one means of lessening the incidence of iron deficiency in early childhood, was evident from both our investigations.

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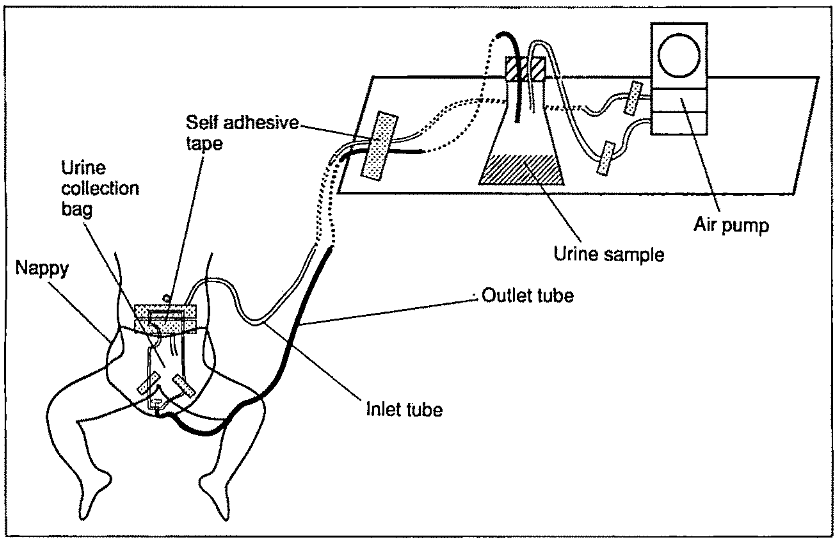
Collecting 24 hour urine samples from children

Sɪʀ,—Collection of urine over several hours for metabolic investigations in infants and toddlers is notoriously awkward: disposable napkins frequently produce contaminated samples, and modified cots are only practicable for small infants.[1 2] The following modified technique imposes few restraints on the patient, and is therefore metabolically accurate, and may be used for accurate collections of up to 72 hours.[3]

A bag is constructed with a narrow tube inlet and a larger outlet. The Hollister 24 hour paediatric urine collection bag is particularly appropriate, having a reinforced outlet provided. The inside pocket of the bag is removed and the bag resealed using a heated bar sealer. A nasogastric tube of approximately 8F guage is inserted 2 cm through a small hole in the top corner of the bag, and sealed in place using spray on plastic adhesive (for example, Dow Corning) and plastic adhesive tape.

The air diaphragm pump (for example, the Charles Austen series), collection vessels, and tubing are attached to provide an air flow of some 3 l per minute, with positive pressure directed into the top of the collection bag, and



Urine collection system.

negative pressure through the collection vessel to its lower end (see fig). For trace element analysis, the tubes, bag, and collection vessel should be rinsed in 0·01N hydrochloric acid, followed by deionised water. Rubber bungs should be avoided as they contain both zinc and iron.

The collection bag is applied with spray on plastic adhesive (Dow Corning). For boys, the penis is drawn into a round hole in the side of the bag, which is then sealed over the scrotum and pubis. For girls, an oval opening is more successful; the seal should include the perineal body. The inlet tube should be secured plastic tape around the lower abdomen, and the free lower end of the bag should be wrapped with a strip of absorbent material, which is changed when the patient passes stool.

The most common complication encountered is urinary leakage, usually the result of the patient playing with the collection bag or tubes. A well fitting nappy and toys attached to the tubes may prevent this complication.

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1 Roberts SB, Lucas A. Measurement of urinary constituents and output using disposable napkins. *Arch Dis Child* 1985;60:1021–4.
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Glucose polymer regimens and hypernatraemia

Sir,—In response to the recent report of hypernatraemia associated with the use of glucose polymer feeds in the management of metabolic decompensation,[1] we would like to report our practice in the management of such cases.

It is well documented that feeds used in metabolic decompensation should not have an osmolality greater than 500 mmol/l.[2] While a generous intake of energy is desirable, fluid and osmolality tolerance will restrict energy provision.

In mild to moderate metabolic stress we advise volumes of oral rehydration solution (Dioralyte, Rorer) and separate drinks of up to 15% strength (w/v) glucose polymer solution. The use of separate solutions eliminates the problems of hyperosmolar feeds and yet provides adequate fluid and a sufficient energy intake over the temporary period of metabolic decompensation. This is generally well tolerated and after 12 to 24 hours the appropriate feed regimen is reintroduced, initially at a reduced strength with regrading to full strength achieved usually by 24 hours.

The authors' reminder of the hazards of hyperosmolar feeding during incidental illness in children with metabolic disease is timely. While glucose polymers have improved the treatment of metabolic disease, their inappropriate use can lead to further complications.

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1 Verber AG, Bain M. Glucose polymer regimens and hypernatraemia. *Arch Dis Child* 1990;65: 627–8.
2 Francis D. In: Francis D, ed. Disorders of amino acid metabolism. *Diets for sick children.* 4th Ed. Oxford: Blackwell Scientific Publications, 1987:282–4.

Ozone in medical gases

Sir,—Ozone is a powerful oxidant and is recognised as causing lung fibrosis if overexposure occurs in adults. We investigated the possibility that concentrations of ozone in medical gases could be such as to be a factor in the development of fibrotic change in lungs in the neonate. Ozone is constantly forming in the atmosphere, particularly in the stratosphere where energetic extraterrestrial photons interact with molecules in the air. Ozone decays continually, normally giving a ground level concentration of around one part per billion.

Cylinders of medical oxygen were analysed using a Dasibi Environmental Corporation model 1108 UV photometric analyser. The limit of detection of the instrument is one part per billion. Six D size oxygen cylinders were analysed, some filled the same day as the analysis, as well as cylinders filled on previous days. In all cylinders no ozone was detected, indicating concentrations of less than one part per billion. During the course of the analysis the ozone concentration of the ambient air in the laboratory was also monitored and readings in the range of 0–6 parts per billion were obtained.

Failure to detect ozone in any of the oxygen cylinders is reassuring, but is not unexpected due to the high reactivity of ozone.

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AUTUMN BOOKS

Nelson Essentials of Pediatrics. Edited by Richard E Behrman, Robert Kliegman. (Pp 743; £25 paperback.) W B Saunders Company (Harcourt Brace Jovanich Ltd), 1990. ISBN 0–7216–2229–1.

One suspects that British paediatricians fall neatly into two camps: those that favour this text's 'big brother' and those that prefer the weightier, although more comfortable British equivalent. This new volume is designed as reading material for the paediatric student/resident—it being too heavy to carry in the white coat, and rather wordy and light on treatment to work as a quick reference manual. How then might one assess this 'half Nelson'?

The star chapter without doubt is the first, covering development and behaviour in a clear and very comprehensive fashion. There is a new (and vastly improved) Denver chart and proper coverage of behaviour, language, hearing assessment, and cerebral palsy. The broad sweeps of the next few chapters—nutrition, genetics, perinatal and adolescent medicine—differentiate paediatrics from adult medicine. These are generally very comprehensive and set up the more standard systematic chapters that follow. The appendix (drug dosage) is very poorly set out in total contrast to the very clear text and line drawings. An added bonus is the reference list at the end of each short section, making it easy for the reader to identify important text rather than struggle through a list of publications at the end of each chapter. Each list also directs the reader to the relevant section in 'big brother'.

The reader is naturally drawn to those chapters which interest him most and I found little to quibble with that would not be explained by transatlantic practice. Having just returned from my annual refresher some of the sections appear slightly out of date but this volume is factually much more complete than its rivals.

A major concern in recommending this valuable text is, however, its North American bias. Drug names, biochemical values, immunisation schedules, and spelling may all lead the unwary examinee into dire trouble with the examiner if this is the sole source of his revision. Despite these drawbacks, it is surprising how well this volume succeeds. Please could we have a 'translation'?

NEIL MARLOW
Consultant senior lecturer

Principles and Practice of Pediatrics. Edited by Frank A Oski, Catherine D DeAngelis, Ralph D Feigin, Joseph B Warshaw. (Pp 2155; $95·00 hardback.) J B Lippincott Company, 1990. ISBN 0–397–50707–0.

This introduces the new challenger for the heavyweight crown of general paediatric textbooks. The challenger weighs 3·42 kg and has a reach of 2100 pages, while the reigning champion—Forfar and Arneil's *Textbook of Paediatrics*—weighs 4·55 kg with a reach of 2050 pages. The challenger is trained by Oski, together with three assistant trainers and 261 helpers.

The book begins with a general section of interesting chapters on, for example, ethics, the scope of paediatrics, the economics of medicine, reading medical literature, and the consultation. Immunology, allergy, and inborn errors are included here, which seems rather inappropriate. The next section concerns the fetus and newborn, with useful chapters on adaptation to extrauterine life, and on intensive care as well as a systematic description of neonatal diseases.

The next 500 pages are devoted to ambulatory paediatrics. The aim of this—that is, non-inpatient paediatrics—is discussed, and its advantages, medical ('the hospital remains a not very safe place for children'), emotional, and financial are stressed. This section includes prevention, chronic illness, developmental problems, abnormal behaviour, emergencies, adolescent medicine, and so on.

The meat of the book (1000 pages) is a comprehensive description of childhood diseases, which it is hard to fault. It is clear, concise, liberally illustrated, and contains many useful tables.

The final part of the book is called 'Important things you forgot to remember'. It is much more than lists of normal values. There is a thoughtful chapter on evaluation of laboratory tests, followed by one on laboratory values. Fifty of the commoner syndromes are described and illustrated, and there is a brief description of some practical procedures. The text ends with lists of the causes of presenting signs and symptoms divided into the common, the uncommon, and the rare.

The presentation of this book is excellent with numerous tables and line drawings. Reproductions of radiographs, computed tomograms, and scans from magnetic resonance imaging are good, and there are many clear clinical photographs. As expected, there are plenty of references, some as recent as 1988, often to comprehensive reviews—for example, one is to 94 cases of neonatal septic arthritis.

This book is written for American paediatricians and at first sight some of the articles might not seem applicable on this side of the Atlantic. However, with implementation of the white paper it seems probable that American problems today will be ours tomorrow. Thus the emphasis on cost effectiveness would warm the Minster's heart.

There is some thoughtful advice we could all heed: we are encouraged to provide a quality service which is caring, compassionate, and personalised. At the same time we are urged to balance our professional life with our family and social lives, and admonished that one's own family should remain a priority. Litigation should be prevented by 'sound medical judgement'. We are however, urged to have an aggressive accountant and obtain a lawyer!

Overall this is a first rate textbook of paediatrics, whose contributors are to be congratulated. It is a very good buy at about half the price of its main competitors.

MARTIN MONCRIEFF
Consultant paediatrician

Otitis Media with Effusion in Children. By David Chalmers, Ian Stewart, Phil Silva, Ann Mulvena. (Pp 167; £18 hardback.) Blackwell Scientific Publications, 1990. ISBN 0–632–02467–4.

Does glue ear matter? More specifically does it affect development? The question is one of great practical importance, as glue ear is a common condition and the insertion of grommets is among the most frequently performed of all paediatric operations. The world literature contains well over 1000 references on the subject, but unfortunately the conclusions they offer are varied and contradictory. This volume by Chalmers and colleagues describes a further attempt to resolve some of the outstanding questions. The authors conducted a longitudinal study of the cohort of children born in Dunedin, New Zealand, in 1972/3. The Dunedin cohort and the investigations based on it are well known to most readers of this journal. It has been one of the most productive of all cohort studies, having resulted already in well over 100 publications in international journals.

The authors set out to overcome many of the criticisms made about previous studies. The relationship between glue ear (properly called 'otitis with effusion') and child development is complex and there are of course multiple other factors that also determine the level of development which a child attains at a particular point in time. In addition, it is very difficult to determine how long a particular child has otitis with effusion and what effect this has on his or her hearing levels during the early childhood years.

The results of this extensive investigation are reported in considerable detail and there is a wealth of information about the background factors for otitis with effusion, the correlation between various diagnostic measures, and the levels of hearing loss associated with the condition.

The conclusion is that bilateral otitis with effusion does indeed affect language acquisition, speech, and behaviour. The differences between the affected children and those without significant middle ear problems are convincing and in most cases are of the order of half a standard deviation.

This study represents a further important contribution to the literature on otitis with effusion and development, but although it is published as a book rather than a paper, it must not be regarded as the last word on the subject. By eliminating many of the methodological flaws of previous studies, the authors have provided support for the view that this condition does indeed affect development. This will perhaps come as no surprise to most paediatricians interested in language development. However, important questions remain; further studies will need to address the early natural history of middle ear disease, the factors which decide whether or not a particular child will be vulnerable to the effects of the condition and the ways in which these high risk children can be identified. It seems highly unlikely that otitis with effusion is a homogeneous condition either in aetiology, in severity, or in chronicity. The hypothesis that some children are likely to suffer much more severely than others from the condition remains to be investigated. New methodological approaches will be required to answer these questions.

This book also contains a comprehensive literature review and many readers will find this invaluable. There is also a summary of the study's main conclusions which, of course, is essential in a book length research report. The chapters which describe the results in detail will probably be bypassed by most readers and will be studied in depth only by those with a personal research interest in this 'sticky' problem.

D M B HALL
Consultant community paediatrician

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Medical problems of ethnic minorities *J Black*
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Pitfalls in clinical diagnosis and the role of investigations *A Redington*
Treatment and outcome of congenital heart disease *W J Brawn*
Mini-symposium 2: Immunological conditions
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669

Review

The cystic fibrosis defect approached from different angles – new perspectives on the gene, the chloride channel, diagnosis and therapy
D. J. J. Halley, J. Bijman, H. R. de Jonge, M. Sinaasappel, H. J. Neijens, M. F. Niermeijer **670**

Endocrinology

Effect of two consecutive administrations of GHRH in children with constitutional growth delay
A. Sartorio, A. Spada, A. Conti, F. Morabito, G. Faglia **678**

Gastroenterology/Hepatology

Gastro-oesophageal reflux and apnoeic pauses during sleep in infancy – no direct relation
J. Y. Paton, U. Macfadyen, A. Williams, H. Simpson **680**

Acceleration of linear growth following intestinal resection for Crohn disease
A. B. Lipson, M. O. Savage, P. S. W. Davies, K. Bassett, W. S. Shand, J. A. Walker-Smith
687

Hematology/Oncology

Agranulocytosis following infectious mononucleosis
S. Sumimoto, Y. Kasajima, T. Hamamoto, T. Miyanomae, Y. Iwai, M. Mayumi, H. Mikawa **691**

Imaging techniques

Herniation of calcifying discopathy in childhood: report of three cases
J. C. Hoeffel, C. Bernard, P. Schmit, L. Denardaud **695**

Echo planar imaging of an infant with pectus excavatum
C. O'Callaghan, B. Chapman, A. Howseman, M. Stehling, R. Coxon, P. Mansfield **698**

Immunology/Allergology

Bare lymphocyte syndrome – combined immunodeficiency and neutrophil dysfunction
N. Will, R. A. Seger, C. Betzler, G. Dockter, N. Graf, M. Büttner, C. Irlé, J. M. Tiercy, F. C. Sitzmann
700

Metabolic diseases

The glycaemic effect of simple sugars in mid-morning and afternoon snacks in childhood diabetes
R. Primavesi, J. Drakeford, D. C. L. Savage **705**

Recurrent, familial Reye-like syndrome with a new complex amino and organic aciduria
O. N. Elpeleg, E. Christensen, H. Hurvitz, D. Branski **709**

Neuroblastoma in a patient with dihydropteridine reductase deficiency
L. G. Greeves, R. J. Leeming, K. Hyland, S. I. Dempsey, D. J. Carson
713

Low-density lipoprotein plasmaphaeresis with and without lovastatin in the treatment of the homozygous form of familial hypercholesterolaemia
J. Thiery, A. K. Walli, G. Janning, D. Seidel **716**

Peroxisomal β-oxidation defect with detectable peroxisomes: a case with neonatal onset and progressive course
P. G. Barth, R. J. A. Wanders, R. B. H. Schutgens, E. M. Bleeker-Wagemakers, D. van Heemstra **722**

Neonatology

Surfactant treatment for respiratory distress syndrome following prolonged rupture of membranes
T. R. J. Tubman, H. L. Halliday **727**

Transient electrocardiographic changes suggesting myocardial ischaemia in newborn infants following tocolysis with beta-sympathomimetics
M. Gemelli, F. De Luca, R. Manganaro, R. Leonardi, F. Rando, A. Agnetti, C. Mami, G. Di Pasquale **730**

Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life
J. S. Jordanov **734**

Pneumology

Parental smoking and asthma in childhood
M. Palmieri, G. Longobardi, G. Napolitano, D. M. L. Simonetti
738

Indexed in *Current Contents*

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Child Health in a Multicultural Society. 2nd Ed. By John Black. (Pp 75; £5·95 paperback.) British Medical Journal, 1989. ISBN 0-7279-0266-0.

'In one of the antenatal clinics where I work they call out the women's names from the files and if the women don't come forward after the second call, they put the file right back to the bottom of the pile. And quite often the way they pronounce the names is completely unrecognisable, and so the women don't go forward and they may wait hours and hours never realising that their names have been called several times' (clinic worker*).

Communication difficulties abound in the health service but are particularly likely with our ethnic minority patients—partly because of language but also because of different views of health and disease. It is with naming systems that we are particularly poor—for example, calling the male child of Jaswinder Kaur, Armarjit Kaur (all Sikh women are named Kaur, all men Singh). This topic plus many others are covered by John Black in his short 75 page paperback. The first two chapters cover the difficulties with living in Britain and contact with health services; many valuable points are mentioned. These include the discrimination the families face, the embarrassment that may arise if children are used as interpreters, the need to allow a parent to sleep in the child's bed if she wishes. In general, Black stresses that we should try to understand something of the family's background and cultural values—and, needless to say to pronounce their name correctly!

The remaining five chapters cover the problems that may be found in individual ethnic groups: Asian, Mediterranean, Chinese, and Afro-Caribbean and African families. A straightforward account is given of the main cultural attributes and naming systems in each group, together with the disease patterns; a useful map illustrates the distribution of sickle cell disease (but is there none in Scotland? The map stops at the border . . .).

This book is a good introduction to a field that is woefully under-represented in medical training, and it should be required reading for paediatric trainees. I would like to have seen more about the health inequalities suffered by ethnic minority groups as a result of racial discrimination (sometimes within the health service), and what as paediatricians we can do to improve the situation. Learning about our patient's country of origin and culture by listening to them is a good start.

A J R WATERSTON
Consultant community paediatrician

*Mares P, Henley A, Baxter C. *Health care in multiracial Britain.* London: Health Education Council, 1985.

Handbook of Neonatal Intensive Care. By Henry L Halliday, Garth McClure, Mark Reid. 3rd Ed. (Pp 404; £9·95 paperback.) Baillière Tindall, 1989. ISBN 0–7020–1399–4.

This familiar pocket book for junior neonatal medical and nursing staff now enters its third edition and inevitably has grown by some 71 pages in the process making it suitable only for the more capacious pocket. The clear layout and presentation has changed little with a number of helpful diagrams. Short nursing points have been appended to several chapters, which are otherwise unchanged, and there have been more major revisions of the neurology, cardiovascular, genitourinary, and metabolic chapters. It is unfortunate that the opportunity has not been taken to update other areas. For instance, the chapter on imaging techniques devotes four pages to M mode echocardiography, but none to cross sectional cardiac scanning, while ultrasound imaging of ischaemic lesions in the preterm infant still only receives seven lines out of 12 pages on cerebral ultrasound. The Siggard–Anderson nomogram is entirely superseded by the microprocessors of modern blood gas machines, and several of the equipment diagrams are of obsolescent or obsolete models. Inclusions and exclusions in such a book will always be a matter of personal preference, but does a page long list of notifiable diseases commencing 'Cholera, plague, relapsing fever . . .' really belong in a handbook of neonatal intensive care, and are 'Guidelines for training towards a career as consultant neonatal paediatrician' and 'Role and functions of regional perinatal centres' appropriate for a book primarily to be referred to in acute situations?

Despite these criticisms this remains an attractive book for the neonatal novice. There is access to a wealth of information through an excellent index. Cross referencing is also extensive and I only managed to uncover one error. Each chapter concludes with a short list of references and suggestions for further reading that seem well up to date.

M DRAYTON
Consultant neonatal paediatrician

Psychiatric Disorders in Children and Adolescents. Edited by Barry D Garfinkel, Gabrielle A Carlson, Elizabeth B Weller. (Pp 569; $33·50 paperback.) W B Saunders Company, 1990. ISBN 0–7216–2612–2.

American child psychiatry, at least in its academic version, has foresworn its earlier allegiance to psychoanalysis and plunged into neuroscience and a more specifically medical orientation. This volume bears witness to the new stance. Many chapters speculate on the relevance of abnormal findings in various neurosciences applied to various diagnostic groupings. Heavy emphasis is placed on classification. Alas, many experimental findings are as yet fragmentary or mutually contradictory but the sense of excitement at a more biomedical approach to child psychiatry comes through well.

Each chapter in this multiauthor textbook tries to integrate scientific studies with clinical practice—usually with success. There are questionnaires, decision trees, lists of indications, and diagnostic criteria (DSM-111-R) sprinkled throughout the text. I thought this was all good stuff, indicating a systematic approach to childhood psychopathology and mental health which some would say is overdue. I also liked the colourful positron emission tomograms and brain maps though these were more scarce. The chapters are well referenced with more acknowledgment of the European literature than is often the case.

This rational approach to assessment, however, is prone to break down when it comes to treatments. There are several times when the text is reminiscent of the unselective enthusiasm of an advocate of alternative nostrums: clomipramine is very effective but some respond well to fluoxetine, lithium helps some, yet others respond to alprazolam, neuroleptics can be useful and there have been reports of a good response to psychosurgery. When this sort of thing starts my optimism about the appearance of systematic approaches withers, but only temporarily. There is good use of case vignettes, which enliven the rather daunting double column pages.

So long as you can read American in comfort this text offers very good reviews of the major topics in classical child psychiatry, written by many of the luminaries in that area and carrying weight accordingly. It will, I hope, becoming a leading text in North America. On this side of the pond, its appeal may be narrower. It is more centred upon the individual child than is much British practice. There is fair but not extensive coverage of liaison psychiatry or psychosomatic problems and comparatively less acknowledgment of the soggy area of social incompetence and privation with which much British child psychiatry becomes preoccupied. These are issues of bias rather than omission (there is a good account of the consequences of parental divorce for instance) and should not detract seriously from its worth. Libraries needing a modern, authoritative mainstream American text should buy it. Psychiatrists will gain from reading it but only the psychoenthusiasts among paediatricians will need to use it for more than reference.

PETER D HILL
Senior lecturer in child and adolescent psychiatry

Early Diagnosis and Therapy in Cerebral Palsy. By Alfred L Scherzer, Ingrid Tscharnuter. (Pp 351: $54 hardback.) Marcel Dekker, 1990. ISBN 0-8247-8109-0.

This book is not about how to make an earlier diagnosis of cerebral palsy. A better title is given in the preface: 'diagnosis and management of the very young child with cerebral palsy'. Written by a paediatrician and physiotherapist, it is probably to physiotherapists that it will have greatest appeal.

The book begins with a brief overview of cerebral palsy, of normal and abnormal neurological development, and differential diagnosis. Neurodevelopment assessment and the management and treatment of the young child with cerebral palsy are then considered in detail, the emphasis being firmly in the Bobath school. An interesting chapter discusses new concepts in treatment related to tactile, proprioceptive, and kinaesthetic input but emphasises the importance of choosing functional treatment goals. The final chapter discusses the assessment of treatment programmes and makes recommendations for developing effective study designs, and the last page reminds us of the need to see treatment in a world perspective.

I do not think the book entirely succeeds in its attempt to 'fill a major need for professionals in bringing together in one source comprehensive information regarding diagnosis and management of the very young child with cerebral palsy'. It does not cover all the aspects of cerebral palsy that are of importance for paediatricians. Not all the chapters have been brought up to date with the same rigour—for example, the section on incidence and prevalence omits reference to studies after 1981.

Early identification remains a diagnostic challenge and there are no solutions here. The section on differential diagnosis is limited.

The index is unhelpful and some of the illustrations, although well chosen, are of poor quality. For the book to fulfill its promise, one would expect some discussion of the problems that may coexist with cerebral palsy. There is no mention of epilepsy, and vision and hearing are inadequately dealt with and out of date.

The book's strength is the discussion of physical management. The chapters on normal and abnormal development, assessment, management, and treatment are comprehensive, but require some cross referencing between the chapters. Some of the descriptions can be hard to follow. One constantly wished to be able to see the movements that are being described—how long will it be before books such as this come accompanied by a video? The limitations of historical approaches to cerebral palsy, with excessive reliance on splinting and orthopaedic surgery are acknowledged, but I was disappointed that there is no discussion of the contribution of modern orthopaedics. There is a very helpful discussion on feeding but nothing on the assessment of nutritional status, the role of the speech therapist and dietitian, or of complicating factors such as gastro-oesophageal reflux.

The final chapter is indicative of the need, even in the most affluent Western societies, to demonstrate the effectiveness of treatment when there is 'a polarization between the advocate and the nonbelievers'; the issues are outlined well.

S J ILETT
Consultant community paediatrician

Textbook of Paediatric Practice. Edited by Y H Thong. (Pp 723; £96 hardback.) Butterworth Scientific Ltd, 1989. ISBN 0–409–49299–X.

Not another textbook of paediatrics! This time it is an Australian one. Or is this an export special that reaches the parts the others haven't already reached? With over 700 pages and a cast of mainly Australian and Chinese contributors this formidable book aims to fill a perceived space in the market, intermediate between the small introduction to paediatrics and the large reference volume.

In parts the approach is disease orientated, describing gastroenteritis and meningitis, whereas other sections have a problem orientated approach with such headings as 'common respiratory symptoms' or 'headache'. A special feature is the series of contributions on subspecialty disciplines impinging on paediatrics. These are mostly surgical areas, but by including radiology, dermatology, and anaesthesia, the book covers most aspects of child health care. The text is thick with information. It has many useful tables and lists, but few line drawings and fewer black and white photographs. Each of the 156 sections has a small number of key references up to 1987. The short section on the telephone interview is a real pearl for anyone who consults by phone, which must be all of us.

There is a marked unevenness in content and approach between sections, even for a multiauthor book. The Glasgow Coma scale appears twice, but with slightly differing nomenclature and numbers of items in the score. Though the index points the reader inquiring after neonatal jaundice to the gastroenterology chapter, this subject is also covered in a rather different manner in the neonatal section. The list of causes of a raised sweat sodium concentration is the most complete I have ever seen, whereas less that half a page is devoted to recurrent abdominal pain. The section on the acutely paralysed child is full of sound practical advice, but the account of child abuse gives no guidance of that sort.

Who is the book for? Its introduction claims a remarkably wide potential readership of students, recent graduates in medicine, nursing and allied health professions, and general practitioners. My student found it rather too large to digest during his eight weeks' paediatrics and claimed it gave him a poor idea of the relative importance of the various conditions. My houseman would find some sections of immense practical help but there are other books which would fit better into his or her pocket. Other texts would be needed for postgraduate diplomas. Aspects of community child health and child abuse would need modification for UK readers and few of us face problems with the blue ringed octopus!

Though this is a magnificent book for quick access to much information it gives the impression of an uneasy compromise aiming for too wide a range of readership. I would pay more and buy the *Textbook of Paediatrics* by Forfar and Arneil for our departmental library.

GERALD McENERY
Consultant paediatrician

Migraine in Childhood. Edited by Judith M Hockaday. (Pp 148; £27·50 hardback.) Butterworth Scientific Ltd, 1988. ISBN 0–407–01590–6.

I recently attended a paediatric meeting during which one of the speakers predicted that more than half of the doctors in the audience would be migraine sufferers. A show of hands quickly confirmed his prediction and simultaneously strengthened one of my prejudices—that doctors are not very accurate in diagnosing migraine. One of my other prejudices is that doctors are not very good at treating migraine. Dr Hockaday's book gives us the opportunity to transform our prejudices about migraine into sensible opinions.

In 'a personal view' at the beginning of the book Dr John Wilson points out that migraine in children is different from migraine in adults. In the first chapter Dr Hockaday expands this theme with a detailed description of the nature of the migraine attack in children. She also discusses the problems of defining migraine. Epidemiologists list criteria which are necessary for the diagnosis of migraine but this 'criterion diagnosis' is unsatisfactory for clinical practice. Dr Hockaday makes two particularly important points for clinicians—firstly the diagnosis of migraine should be by exclusion (that is, think about the differential diagnosis), secondly it should be longitudinal (that is, allow enough time for a recognisable pattern of symptoms to emerge).

Dr Hockaday's first chapter sets the tone for the rest of the book. She writes clearly and logically displaying an extensive knowledge of the literature. The next chapter by Ziegler deals with epidemiology and inheritance—headache is a very common symptom in children whereas migraine, if narrowly defined, is less common but still affects perhaps 3–5% of the population. The difficulty of defining migraine narrowly is shown by reading Gwilym Hosking's chapter on the variants of migraine in childhood. He has the task of explaining such terms as 'complicated migraine' and 'migraine accompagnée or associée' and I'm relieved to report that he enlightens rather than confuses. If you want to know about hemiplegic migraine, basilar artery migraine, ophthalmoplegic migraine or the 'Alice in Wonderland syndrome' then this is the chapter for you. In the next chapter Dr Hockaday returns to define 'migraine equivalent', to talk about migraine without headache, and to discuss the validity of the diagnosis of abdominal migraine in children.

The book continues with sensible sections on the management of childhood migraine, a description of paroxysmal disorders which may be confused with migraine (do you know about alternating hemiplegia of childhood?), and a guide to those difficult areas where migraine and epilepsy apparently overlap. Finally there is an excellent review of the literature on the pathophysiology and precipitants of migraine—everything from 'the spreading depression of Leão' to oligoantigenic diets and the distress about stress.

This is not just a book for paediatric neurologists. I recommend it to all paediatricians and to general practitioners. It is well written by people who understand the subject and who are constructively critical of the literature. It is not too long and for those who are really interested in further reading there are 21 pages of references. It is slightly repetitive but this seems inevitable if each of the chapters is to stand on its own. I was so convinced of the book's merits that I had already purchased it by the time I was sent a copy to review—what better recommendation than that?

C M VERITY
Consultant paediatric neurologist

Treatment of Infants, Children and Adolescents. Edited by Fredric D Burg, Robert E Merril, Robert J Winter, Deborah H Schaible. (Pp 406; £15·50 paperback.) Harcourt Brace Jovanovich Ltd, 1990. ISBN 0–7216–2139–2.

This is the first book review I have undertaken and in the accompanying letter the editor requests a sparkling first paragraph. This I find difficult as this is a very factual book, being extremely lucid and concise. It is wider than the title suggests, covering the aetiology, signs, symptoms, as well as management of many conditions. There is also a neonatal chapter.

The book is divided into three sections; the first considering the differential diagnosis of presenting symptoms and signs with advice regarding management. This is very well tabulated with a column for discriminating features and brief notes on treatment and key points. The middle and largest section covers diseases affecting the childhood and adolescent population, which overall is set out extremely well and has 20 sections covering the usual systems. I found the sections on cardiovascular and dermatological disorders particularly useful. The section on mental and emotional disorders was interesting, dealing with a wide range of topics including areas of disturbed adolescent behaviour such as suicide, smoking, drug use, and alcoholism, of which paediatricians in this country generally have limited experience.

The final section is a drug formulary and details dosage, routes of administration, side effects, and interactions. The authors state that they hope to update this regularly and this section will require revision at least every two years.

There are four editors and 55 contributors to this book and all practise in the United ates. Despite the many authors the sections l have a remarkable uniformity. Parts of the ction on pulmonary disorders are more rbose than the rest of the book and more ts here would be helpful. This book is aimed junior paediatric staff, I think, and perhaps ctions on innocent murmurs and sudden fant death syndrome would be helpful when e text is updated. This book will also be of gnificant value to consultants in this country the information is very up to date, although e small print is a disadvantage with the lvancing hypermetropia of age.

Overall there is a great deal of valuable formation in this book which is easy to tract and each section has pertinent and cent references. The price is inexpensive d I would recommend this book to both nior and senior medical staff practising ediatrics in any part of the developed world.

D S K BROOKFIELD
Consultant paediatrician

eaching Genetics to Medical Students. A rvey and Recommendations. Report of a orking Party of the Committee on Clinical enetics. (Pp 32; £7 paperback.) The Royal ollege of Physicians of London, April 1990. BN 0–090096–96–1.

working party of the Committee on Clinical enetics of the Royal College of Physicians s produced a well researched and revealing port on the existing teaching of genetics in K medical schools and drawn up recom-endations for the future. It is now fairly ear why many doctors, however newly alified, have difficulty interpreting pedigree ks or understanding chromosome reports: netic teaching at present is often inadequate d should be improved. The report has und marked variation between schools and und that on average there is only 5·57 hours timetabled genetics teaching in the clinical urse and 17·35 hours in the preclinical urse (when two exceptional centres with 66 d 50 hours respectively are excluded).

The report has drawn up guidelines for a lanced genetics syllabus. This is based on a estionnaire sent out to 429 clinicians and edical teachers from all specialties. They ere asked for their opinion on essential netic topics and basic genetic skills to be hieved by qualification. Response was high d interestingly there was significant agree-ent among responders irrespective of ecialty.

The report recommends that clinical geneti-ts should play a larger part in coordinating netic teaching throughout the five year ining of undergraduates. This would event unnecessary repetition and help phasise the clinical relevance of the subject. acknowledges that more clinical geneticists ll be necessary to implement their proposals t the Working Party hopes to help by tting up a Genetic Education Task Group. is could coordinate teaching at a national el and provide teaching aids, access to ofessional teachers, and workshops for nicians involved.

The findings of the report provide strong pport for more and improved teaching of netics to medical students and highlight the ed for medical schools to match the revolu-n in clinical genetics which is taking place at moment.

KAREN TEMPLE
Consultant in
clinical genetics

Paediatric Pathology. 2nd Ed. Edited by Colin L Berry. (Pp 830; DM 380 hardback.) Springer-Verlag, 1989. ISBN 3-540-19536-X.

Diseases specific to the paediatric period are intimately related to the processes of growth and development and thus tend to be expressed at the time when development progresses most rapidly in fetal and early neonatal life. Scientific and diagnostic advances have moved inexorably towards the point of inception of disorders such as structural and biochemical anomalies in the embryo and immature fetus. To many non-medical and some medical people the terms perinatal pathology and paediatric pathology have become virtually synonymous. There is thus an almost insurmountable problem in presenting an overview of a subject which is so heavily weighted towards the fetal end but contains important conditions that present only in infancy or childhood.

This task is one that is now attempted only by Professor Berry, whose book thus occupies a unique position. How has Professor Berry faced up to the advances in fetal and perinatal pathology in producing a second edition? The new edition is as well produced and illustrated as the original and is clearly written throughout with an increase in length by some 130 pages. The book has not changed in overall emphasis, perhaps because neither editor nor many of the contributors are practising paediatric pathologists.

In the first chapter, on examination of the fetus, there is a new section on the neonatal necropsy and a few additional tables to aid in determining fetal maturation. The chapter on the placenta has been excluded in favour of a new chapter by RO Kaschula on infectious diseases. The rest of the book has been updated to varying levels by the original authors. Although some chapters, such as those on the respiratory system and sudden unexpected death, are replete with recent references, others contain relatively few references to work published within the last 10 years. Surprisingly, the new chapter on infectious diseases, while dealing at length with congenital syphilis, contains no mention of AIDS, although the topic is touched on briefly elsewhere in the book.

Many of the chapters in this text are good introductory reviews of the subject and some are extremely useful for reference purposes. The work as a whole remains in that indeterminate position as neither an everyday bench book for the practising pathologist nor a comprehensive academic reference book on paediatric pathology. It is a work for the departmental or hospital library rather than individual purchase.

J S WIGGLESWORTH
Professor of perinatal pathology

Principles and Practice of Endocrinology and Metabolism. Edited by Kenneth L Becker *et al* (Pp 1944; $125 hardback.) JB Lippincott Company, 1990. ISBN 0-397-50759-3.

With nine editors, 305 (largely American) authors and nearly 2000 closely typed pages one would be disappointed if this book did **not** prove to be the comprehensive source text intended by Professor Becker and his colleagues! The only practical approach to a review of such a tome for this journal was to see if it fulfilled such a remit for a paediatrician with an interest in endocrinology.

The work is laid out in a disease oriented format with specific chapters on anatomy, physiology, and pathology within the affected system. Each section includes a chapter on the paediatric aspects of each condition where appropriate. This design means that it is often necessary to look in several places to gain the desired information, but the index is extremely comprehensive. There is little historical information and the references are very topical.

Although references are provided at the end of each section, paediatric endocrinologists will find the coverage of their interest rather skimpy and lacking in discussion of the more current controversies and research. For instance, there is very little concerning nonconventional indications for growth hormone treatment or the surgical approaches to short stature in skeletal dysplasias. The therapeutic options for juvenile thyrotoxicosis are mentioned but not assessed critically. For a clinician used to focusing on the impact of an endocrinopathy on the rate of growth the section on auxology is also disappointing. Many of the named drugs are given as their American equivalents and SI unit conversion factors are only given in an appendix. The doses for children are often stated baldly, without allowance for body size or individual variation.

The book succeeds best as a reference for those seeking information outside their usual field of interest and those needing an up to date account of the physiological and metabolic basis for a disease process. There is also entertaining coverage of some extremely rare conditions (such as 'hamburger thyrotoxicosis' secondary to the ingestion of thyroid gland included in mincemeat from one abattoir) and some high quality black and white illustration.

At only $125, which puts the cost of many comparable recent British editions to shame, this reference text should find its way on to the shelves of our libraries as a source book for a wide range of clinicians and scientists. A paediatrician wishing to own a definitive textbook specifically relating to endocrinology in childhood might find the second edition of Brook's *Clinical Paediatric Endocrinology* a more appropriate choice.

J K H WALES
Honorary senior lecturer

Operative Paediatric Urology. Edited by J D Frank, J H Johnston. (Pp 256; £80 hardback.) Churchill Livingstone, 1990. ISBN 0-443-034788.

Operative Paediatric Urology raises the technical manual to the level of an art form. David Frank and Herbert Johnston have produced a beautiful account of the open operations of the specialty. The text is concise, the layout stimulating and the illustrations, to the surgical eye at least, visually pleasing. The illustrator, Philip Wilson, should be credited for his contribution to the success that this book will undoubtedly enjoy. Paediatric urology is breaking new ground. The editors have endeavoured to reflect this in their choice of subjects and authors. The powerful influence of Liverpool upon the specialty is clearly evident. Mr Johnston has contributed a number of chapters himself and his successor at Liverpool has written an excellent chapter on urinary diversion. There are also excellent contributions from some of the many distinguished Americans who spent time as visiting fellows there.

The topics range from the humble circumcision (an operation which nevertheless is often badly performed) to the technical *tours de force* of cloacal reconstruction and exstrophy closure. Dr Duckett on hypospadias, Dr Pena on persistent cloaca, and Mr Mundy on cystoplasty are just a few examples of the many chapters written by acknowledged masters of their field. The 'bread and butter' operations of paediatric urology are also well served by excellent chapters on pyeloplasty and ureteric reimplantation. The surgery of Wilms' tumour and congenital adrenal hyperplasia is also well covered. Surgeons are individualists and it would be surprising if one could not find points to quibble about. A more serious criticism relates to the limits that the editors have imposed upon themselves. In their wish to avoid a 'multivolumed encyclopaedia' they have omitted descriptions of endoscopic techniques. This is a pity. The average reader might reasonably have turned to this book for guidance on endoscopic urethral surgery, laparoscopy, and possibly the submucosal Teflon injection (STING) technique for correcting reflux. Surgical procedures for the treatment of urinary calculi have been excluded—on the grounds that adult urologists will already be familiar with these. Perhaps so, but paediatric surgeons may not be and paediatric surgeons surely represent a sizable section of the market this book will be aimed at. Other omissions include ureteric plication procedures, the valuable Mitrofanoff operation, and artificial sphincter surgery.

Every surgeon who operates on the paediatric urinary tract will value this beautifully illustrated book—but many will wish that the coverage of the subject had been more complete.

D F M THOMAS
Consultant paediatric urologist/surgeon

Your Child with Congenital Adrenal Hyperplasia. By G L Warne. (Pp 32; $8 paperback.) G L Warne, 1989. ISBN 0–7316–5816–7. (Requests to: Department of Endocrinology and Diabetes, Royal Children's Hospital, Parkville, Victoria 3052, Australia.)

Surveys suggest that the general public, although showing a great interest in medical and scientific topics, have in fact a poor understanding. Giving parents insight into the underlying basis of their child's medical problem can be difficult but rewarding. Booklets explaining childhood disorders are a useful aid to families, and well established in clinical practice. The available literature is now extended to include 'Your child with congenital adrenal hyperplasia'.

This is a bright attractive book written for parents in simple language, well illustrated with colourful diagrams and cartoon pictures. The contents include an introduction about the adrenal gland, the biochemical disorder in congenital adrenal hyperplasia, maintenance and emergency treatment, the cause and management of virilisation, comments on inheritance, and prenatal treatment. Topics are tackled concisely, but readers without any medical or scientific background will have difficulty understanding some sections. The function of adrenal enzymes, or the sexual differentiation of the fetus, will always require a careful patient explanation from a paediatrician with an interest in this area.

Undoubtedly some parents will not attempt to read this book and others will only derive limited benefit from it. However, it should be available in any clinic treating children with congenital adrenal hyperplasia as a valuable supplement or stimulus to discussion.

D J CARSON
Consultant paediatrician

Down Syndrome—The Facts. Edited by Mark Selikowitz. (Pp 197; £5·95 paperback (£10·95 hardback)). Oxford University Press. 1990. ISBN 0–19–261901–2 (0–19–261872–5).

For parents facing anxiety and disbelief at being told that their child has Down's syndrome, this easily read paperback would provide some answers to the myriad of questions resulting from their emotional turmoil.

The book begins with a comprehensive range of reactions which may be experienced by the parent, offering some reassurance that their feelings are not unusual. There are straightforward biological explanations of the condition, a grasp of which helps parents greatly in coming to terms with the situation.

There follows an introduction into the health and development of children with Down's syndrome, with information about the various educational pathways which may be available.

For the more distant future, the book outlines the rapidly changing attitudes of society to people with intellectual disability, emphasising increasing opportunities for employment and social integration.

The positive style in which the book is written does much to encourage parents to begin the task of giving the love and support essential to their child's future.

If the book has any irritations, it is the occasional feeling that 'doctor knows best'. Many parents of handicapped children require explanations of the reasoning behind any advice given; this enables them to take a more active role in making important decisions as to the most appropriate course to follow for their child.

RICHARD BURDEN
Parent

Metabolic Bone Disease in Children. Edited by Salvador Castells, Laurence Finberg. (Pp 408; $119·50 hardback.) Marcel Dekker, 1990. ISBN 0-8247-8153-8.

Metabolic bone disease is not a common problem in general paediatrics but it is impossible to avoid it entirely. The spectrum of subspecialty interest in bone disease is illustrated by the diverse background of the 30 contributors to this book. The clinically orientated chapters are interesting, although a little repetitive. Topics covered include the various causes of rickets, hyper-responsiveness to vitamin D, osteopetrosis, osteoporosis, osteogenesis imperfecta, and skeletal dysplasias. The short chapter by the late Harold Harrison was especially clear and his characteristic style of including case histories could have been adopted by other authors with good effect. The more scientifically orientated chapters on vitamin D, circadian rhythms, and resistance to vitamin D are probably of less interest to the clinician. The researcher may also be disappointed for although the scientific developments are well covered, none of the 1200 references have been published within the last three years.

A lot of information is made available in this relatively small but expensive book. It may be of interest to some paediatricians some of the time but will not suit any group all, or even most, of the time. Those paediatricians with subspecialty interests in metabolism, nephrology, neonatology, genetics, and orthopaedics will have more extensive sources of information already available to them.

D J CARSON
Consultant paediatrician

Respiratory Illness in Children. 3rd Ed. By Peter D Phelan, Louis I Landau, Anthony Olinsky. (Pp 403; £59:50 hardback.) Blackwell Scientific Publications, 1990. ISBN 0-632 02567-0.

All paediatricians see and manage many children with acute and chronic chest disease and this book provides an excellent and comprehensive account of both common and uncommon paediatric respiratory disorders. This is the third edition in not many years and illustrates, not only the increased awareness and importance of respiratory illness in children, but also the advances in better understanding and treatment. It originates from perhaps the leading paediatric respiratory department in the world and combines a scientific and practical approach; much of the objective data comes from their department with the clinical and therapeutic advice being based upon the authors' own extensive clinical experience. The format of this book is similar to the previous editions, with the chapters on epidemiology of respiratory infections and asthma, the management of asthma, and cystic fibrosis being updated and providing a 'state of the art' account.

Other chapters cover neonatal disorders, suppurative lung disease, tuberculosis, rarer lung diseases, congenital malformations, and a new chapter on lung defences and infection in the compromised host. There are useful chapters on respiratory noises and cough; even the chapter on physiology is not too difficult to follow and should be read by candidates preparing for the higher examinations.

All paediatricians, whether in hospital or the community should have access to this book. Indeed, if this were so, the work load of one paediatric respiratory physician would be reduced.

P H WELLER
Consultant paediatrician

Current Perspectives in Paediatric Urology. Edited by Robert H Whitaker. (Pp 124; DM 150 hardback.) Springer-Verlag, 1989. ISBN 3-540-19563-3.

Those who yearn for the return of Victorian standards may remember there were days when all surgical procedures in children were performed by dedicated general surgeons. Then came paediatric surgeons, making great strides, in the surgical management of children. Today we are witnessing the emergence of the specialist. Not the specialist of 'single or double seater' fame, but the skilful and thoughtful surgeon, giving helpful advice about difficult areas of surgical practice. In this book, a 'coven' of eminent paediatric urologists review a simmering cauldron of contentious issues and produce helpful advice about many difficult problems.

There are topics which will interest general paediatricians, as well as nephrologists, and urologists. The chapters discussing ureteric reflux and the difficult decision surrounding ureteric reimplantation clearly outline contemporary opinions. It is of interest to see attention being focused once more on the role of bladder dysfunction as a potential cause of renal damage. The issues of prenatal diagnosis and the contentious issue of prenatal diagnosis of urinary tract abnormalities will be of interest to all paediatricians. The criteria for termination of pregnancy are clearly defined. The wisdom of discouraging fetal surgery except in one or two specialist centres is to be applauded.

The management of other congenital abnormalities including pelviureteric junction obstruction, prune belly syndrome, and renal dysplasia is discussed. The difficulties of interpreting the isotope renograms in equivocal upper tract dilatation adds to the problems of management of equivocal upper tract dilatation. The differential diagnosis of Wilms' tumour will be helpful. Despite the good overall results of its treatment, it is sad to learn that one third of patients with renal tumours are still not treated in major oncological centres. The chapter about the confusing problems of intersex contains a useful classification, with practical advice about its diagnosis. The major advances in the management of urinary incontinence and the neuropathic bladder are outlined, and provide a helpful guide to those treating children with these awkward problems.

Although this is a book written by urologists, details of surgical techniques do not predominate yet there is sufficient detail.

This is a clearly written book, providing information which brings the non-specialist up to date with contemporary opinions in paediatric urology. It is recommended reading for all those with an interest in the problem of the urinary tract.

J T BROCKLEBANK
Consultant nephrologist

Dictionary of Medical Syndromes. Edited by Sergio I Magalini, Sabina C Magalini, Giovanni de Francisci. (Pp 1056; $79·50 hardback.) J B Lippincott Company, 1990. ISBN 0-397-50882-4.

Perhaps the best place for this large, hardback dictionary of medical syndromes is somewhere near the telephone. Thousands (>2700) of syndromes, eponyms, and odd medical phrases are defined and can be easily looked up.

The authors, from the departments of surgery and anaesthetics at the Universita Cattolica del Sacro Curore in Rome, have put together a massive amount of information. The word 'syndrome' in the title is used in its broadest sense. The book covers conditions not included in standard genetic, medical, or surgical texts, and, perhaps for this reason, could prove helpful. It is not exactly clear who this book is aimed at. I found the eponyms interesting, particularly from a historical perspective, but I am not sure of the relevance or usefulness of some of the entries. I doubt whether anyone would look up 'Leaking duodenal stump' or 'choriocarcinoma' in a book about syndromes. The book was used for a week in our genetic department and inevitably there were some omissions, poor cross referencing, and odd classifications. However, a lot of detailed useful information was also given. There are subheadings for synonyms, signs, (a)etiology (all text is in American), pathology, diagnostic procedures, therapy, prognosis, and bibliography. The information might have been simplified by concentrating on signs, symptoms, and aetiology, as the rest of the book can become outdated so easily. For just this reason, I worry about accuracy of the text in places, and no one would rely solely on a dictionary of syndromes to offer appropriate treatment for a condition. Inclusion of references helps to get round this problem and is very useful as it allows the reader access to the original literature.

Used as a guide by an experienced clinician, able to recognise the occasional mistake, the book has potential, and I am sure it will find its place in our library alongside other reference books. In the hands of an inexperienced student, however, it could be misleading. I think there is still a place for books of this kind, even in the age of the computer. Many of us still prefer them, although a lot of information is lost in this form. Perhaps the next edition should come out on floppy disk, allowing the reader the possibility of indexing on key words rather than syndrome title only.

KAREN TEMPLE
Consultant in clinical genetics

CURRENT RESEARCH THEMES

Junior staffing cuts in paediatrics—American style

If you've had a surfeit of JPAC, career or visiting registrars, and working hours, and think these are purely NHS problems, you should read the article by Honigfeld *et al* (*Pediatrics* 1990;**85**:969–76) about strategies used by American hospitals faced with coping without paediatric residents. Apparently some hospitals there are finding it difficult to comply with training requirements, some are cutting back for financial reasons, and some are in difficulty because of reductions in the hours residents are permitted to work. Strategies to plug the gaps have included getting other people to do more (nurses, medical students, family practice residents, the remaining paediatric residents, and paediatricians), hiring more staff, and hiring locums. Some of the options were restricted in practice—if there's a shortage of nurses it's unrealistic to think they can take over many of the doctors' duties.

None of the solutions seemed entirely satisfactory and the authors comment that 'physicians generally agreed that residents are the optimal hospital staff provider'. The authors do not address the question of the quality of care provided by the 'gap pluggers' and the work offers no solutions to staffing problems in British hospitals, but at least we are not alone.

Risk to SIDS siblings

Good news is uncommon enough for us to want to cling to it. What a relief it was when Peterson *et al* reported (*J Pediatr* 1986;**108**: 911–4) that first in Norway and then in Washington State they had found no significant increase of SIDS in the siblings of victims. How disappointing, then, to read a recent report, again from Washington State (Guntheroth *et al*, *J Pediatr* 1990;**116**:520–4) giving a 1·3% risk of SIDS in siblings, six times that in the general population. Estimates of relative risk quoted in the literature vary between 3·4 and 10 so that despite some variations in the populations compared it seems that we will have to accept that the siblings are at increased risk. This study also showed a sixfold increase in risk of death in infancy in the siblings of infants who died from causes other than SIDS. When a baby died a non-SIDS death there was an increased risk of non-SIDS death but not of SIDS in subsequent siblings, but when a baby died of SIDS subsequent siblings were at increased risk of both SIDS and non-SIDS deaths and the overall risk of death in those siblings was 2%.

Racial differences in SIDS

The low incidence of SIDS in Hong Kong was pointed out by Davies[1] and it has been suggested that nursing babies supine, as is the tradition there, may be protective.[1 2]

A paper from California in the same edition of the *Journal of Pediatrics* (Grether *et al*, *J Pediatr* 1990;**116**:525–8) looks at Americans of Japanese, Chinese, Filipino, Korean, and Vietnamese origin. The incidence of SIDS varied from 0·9 to 1·5 per 1000 and was significantly higher in the groups which had been longer in the United States. The same authors had previously reported an incidence of SIDS among Chinese babies in California that was 38 times that found by Davies in Hong Kong.

Whether these differences are environmentally or culturally determined, or whether there is something about people who emigrate which makes them more prone to SIDS than those who stay put, is not known. Do the Chinese in California lie their babies prone?

1 Davies DP. Cot death in Hong Kong: a rare problem. *Lancet* 1985;ii:1346–8.
2 Engelberts AC, de Jonge GA. Choice of sleeping position for infants: possible association with cot death. *Arch Dis Child* 1990;**65**:462–7.

Severe neonatal respiratory failure

Extracorporeal membrane oxygenation and carbon dioxide removal for the management of severe acute respiratory failure has been on the horizon for some years now but its application to the newborn has been slow. A report from Paris (Chevalier J-Y *et al*, *Lancet* 1990;**335**: 1364–6) describes the use of this technique in 20 newborn babies, 17 of whom survived with no apparent deficit in lung or brain function. The babies were all of more than 35 weeks' gestation and weighed more than 2000 g and the causes of their respiratory failure were: persistent pulmonary hypertension of the newborn (n=7), meconium aspiration (n=5), sepsis (n=5), respiratory distress syndrome (n=2), and diaphragmatic hernia (n=1). None had been expected to survive with conventional management.

Are we about to witness another revolution in neonatal intensive care?

Phenobarbitone is a depressing drug

Do we need any more nails to hammer into the coffin of phenobarbitone as a treatment for childhood epilepsy? If so, what about depression? Brent and colleagues in Pittsburgh report on the follow up of 28 patients aged 6 to 16 years treated with a single drug for epilepsy (*Pediatrics* 1990;**85**:1086–91). Major depression was diagnosed in 38% of phenobarbitone treated patients and none of those treated with carbamazepine. Discontinuation of phenobarbitone treatment led to recovery from depression. Strangely the frequency of suicide attempts was the same (phenobarbitone 13%, carbamazepine 12%) in the two groups. The authors do not say whether any of these attempts were successful and do not distinguish between determined attempts at suicide and 'cries for help'. They point out that the small study numbers and the non-random assignment to the two drugs precludes firm causal conclusions.

Latent coeliac disease

There are those who have coeliac disease and there are those who don't. At least that's the way its been looked at until recently, but now the concept of latent coeliac disease needs to be incorporated into thinking about basic mechanisms of the disease. O'Mahony and colleagues in Edinburgh (*Lancet* 1990;**335**: 1487–90) studied eight adult patients with dermatitis herpetiformis and normal jejunal histology (most patients with dermatitis herpetiformis show the histological changes of coeliac disease). Measuring immunoglobulins and antibodies in jejunal fluid they found changes similar to those found in untreated coeliac disease, that is, raised IgA, IgM, and IgG and high concentrations of IgA and IgM antibodies to gliadin, β lactoglobulin and ovalbumin. Serum concentrations of IgA gliadin antibodies were the same as in controls but those of IgG antibodies were intermediate between those found in controls and in patients with coeliac disease.

Latent coeliac disease may be found in apparently healthy people, first degree relatives of patients with coeliac disease, people with recurrent aphthous ulceration, and in gluten sensitive diarrhoea without overt enteropathy. The changes in antibody secretion into the gut are probably a marker of susceptibility but a further insult seems necessary if the latent disease is to progress to enteropathy with characteristic histological changes. The elucidation of the nature of that insult will be an important part of future research into adult coeliac disease and the relevance of the findings for the disease in children will need to be considered.

ELISA's baby and the diagnosis of tuberculous meningitis

We all know ELISA (enzyme linked immunosorbent assay), of course, and a very good friend she's been. In the diagnosis of tuberculous meningitis, however, detection by ELISA of antimycobacterial antibodies in cerebrospinal fluid gives inadequate accuracy. Now workers at the Karolinska Institute in Stockholm have developed a method for counting cells in blood or cerebrospinal fluid that are secreting antigen specific IgG or IgA antibodies—a nitrocellulose enzyme linked immunospot assay—and the method has been used at the Shanghai Medical University to examine cerebrospinal fluid and blood from patients with tuberculous meningitis (Lu *et al*, *Lancet* 1990;**336**:10–3). In previously reported studies the Swedish team has shown the technique to be useful in the diagnosis of Lyme disease and they have demonstrated cells in the cerebrospinal fluid secreting myelin antibodies in people with multiple sclerosis.

Twenty five patients, adults and children, had a clinical diagnosis of tuberculous meningitis. Cerebrospinal fluid was examined from all of them and cells secreting anti-BCG IgG antibodies were found in 24. Doing the test on blood was less reliable. Five patients with a positive cerebrospinal fluid IgG test had blood examined. Two had IgG antibody secreting cells and four had IgM antibody secreting cells in blood. Six patients had cerebrospinal fluid examined within a week of the onset of symptoms and five had anti-IgG antibody secreting cells. Maximum numbers of the cells were found in the second and third weeks of the disease. Cerebrospinal fluid was also examined in 12 patients with bacterial, cryptococcal, or viral meningitis and one sample, from a patient with cryptococcal meningitis, contained anti-BCG IgG secreting cells.

Nineteen of the 25 patients had raised cerebrospinal fluid concentrations of anti-BCG IgG antibody measured by ELISA, five of the six negative tests occurring in the first week of the disease and the other in the second.

As a parting shot the authors mention the possibility of using the polymerase chain reaction (PCR) to detect mycobacteria in the cerebrospinal fluid and call for comparative studies of PCR and the immunospot assay.

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ARCHIVES OF DISEASE IN CHILDHOOD

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V CM

Annotations

1193 Hearing screening in children—state of the art(s) *M P Haggard*
1196 The genetics of deafness *William Reardon, Marcus Pembrey*
1198 Postviral fatigue syndrome *B Lask, M J Dillon*

Original articles

1199 Endocrine function and morphological findings in disorders of the hypothalamo-pituitary area *Emanuele Cacciari, Stefano Zucchini, Gabriella Carla', et al*
1203 Increase in urinary growth hormone excretion in puberty *D A Price, G M Addison, E D Herbert*
1205 Assessment of gonadal maturation by evaluation of spermaturia *Franz Schaefer, Joachim Marr, Christoffer Seidel, et al*
1208 Indices of intact serum parathyroid hormone and renal excretion of calcium, phosphate, and magnesium *N J Shaw, J Wheeldon, J T Brocklebank*
1212 Helicobacter pylori and associated duodenal ulcer *C K Yeung, K H Fu, K Y Yuen, et al*
1217 Severe hypertension after liver transplantation in α_1 antitrypsin deficiency *G Noble-Jamieson, N D Barnes, S Thiru, et al*
1222 Corticosteroids in primary tuberculosis with bronchial obstruction *M Toppet, A Malfroot, M D Derde, et al*
1227 Virological investigations of acute encephalopathy in India *Rashmi Kumar, Asha Mathur, Arvind Kumar, et al*
1231 Perianal appearances associated with constipation *U Agnarsson, C Warde, G McCarthy, et al*
1235 Ventilator dependency in the United Kingdom *R O Robinson*
1237 Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus *Henriëtte A van Steensel-Moll, Jan A Hazelzet, Edwin van der Voort, et al*
1240 Effects of newborn screening of cystic fibrosis on reported maternal behaviour *Carol Boland, Norman L Thompson*
1245 Central nervous system vasculitis after chickenpox—cause or coincidence? *Avinoam Shuper, Eileen P G Vining, John M Freeman*
1249 Reproducibility of 24 hour oesophageal pH studies in infants *F J Hampton, U M MacFadyen, H Simpson*
1255 Bronchial asthma and acid reflux into the distal and proximal oesophagus *P M Gustafsson, N–I M Kjellman, L Tibbling*
1259 Air leaks and vasopressin release *N McIntosh, P Prakash, A Smith*
1263 Recognising failure to thrive in early childhood *A G K Edwards, P C Halse, J M Parkin, et al*
1266 Use of thermographic imaging to study babies sleeping at home *E S Anderson, M P Wailoo, S A Petersen*
1268 Continued need for pneumococcal prophylaxis after splenectomy *I A Murdoch, R Dos Anjos*
1269 Visceral leishmaniasis in a Scottish child *P Galea, K M Goel*
1270 Crohn's disease of the lung *J W L Puntis, M J Tarlow, F Raafat, et al*
1272 Topical anaesthesia for repair of minor lacerations *D H Bass, P J Wormald, J McNally, et al*
Commentary *D P Drake, P A Dale*
1274 Lymphocytes bearing the T cell receptor $\gamma\ \delta$ in human breast milk *A Bertotto, G Castellucci, G Fabietti, et al*
1275 Intravenous immunoglobulin in virus associated haemophagocytic syndrome *P Goulder, D Seward, C Hatton*

Regular review

1278 Helicobacter pylori *B Drumm*

Current topic

1283 The cytokines are coming *Kevin P Windebank*

Personal practice

1286 Head injury—how community paediatricians can help *Marion Crouchman*
1287 **Letters to the editor**

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Annotation

Hearing screening in children—state of the art(s)

General principles of screening

Many of the 10 Wilson-Jungner principles of screening[1] are now widely familiar, even among those who cannot recite them all or attribute the source. The principles refer to the need for acceptable tests that will predict with reasonable accuracy during its asymptomatic stage the presence of a disease (or of an impairment that will lead to a disability) to the necessary availability of acceptable effective treatments, and to various other ethical and practical prerequisites for screening asymptomatic populations. These principles have never been seriously challenged, although there is reason, when exploring fast moving fields or when the objective is the secondary prevention of disabilities, to avoid applying them over literally. Current reappraisals of child health surveillance[2] and further ethical considerations[3] urge four additional principles:

(xi) The incidental harm done by the screening, and by the information (correct or otherwise) that it gives, should be small in relation to the total benefits from the screening-assessment-treatment system.

(xii) There should be agreed guidelines on whom to divulge the provisional and the final results to, and on when and how this is best done; there should be transitional counselling support where necessary.

(xiii) All screening arrangements should be reviewed from time to time in the light of changes in demography, culture, health services, technologies, and the epidemiology of the target conditions.

(xiv) Because 'cases' are not homogeneous, the balance of costs, benefits, and risks from screening, assessment, and treatments has to be worked out on a stratified (demographic or case type) basis, and the definition of the target group has to be revised so that this balance is favourable for all strata within it.

Reflection on the 14 principles leads to a more cautious approach to screening than has recently prevailed in some quarters.

Subject to three qualifications of degree listed below, severe profound prelingual hearing impairment does satisfy the principles; screening for otitis media with effusion would require a lenient reading of several of them. Incomplete, but coherent and scientifically underpinned, evidence indicates that early fitting with hearing aids is advantageous for linguistic and cognitive development in permanent hearing loss.[4] Early detection is therefore an appropriate public health goal, potentially to be achieved by some form of surveillance such as a screen.

In practice the three most important principles affecting screens of hearing concern the availability of suitable screening tests, of audiological assessment, and of effective treatment. Test methods have to be predictive but simple, inexpensive, and robust. The high requirement for skilled interaction and the difficulty in achieving cooperation of young children entail that screening by behavioural tests between about 1 year to about 4 years of age cannot be robust; this has not stopped some authorities employing undertrained staff, or misemploying highly trained staff, in behavioural screening within this age range.[5] In post-screen assessment, measurement of the hearing of most children at any age is feasible, although even here obtaining accurate results on very young or uncooperative children is resource intensive, and not always an option, given the gross shortfall of trained paediatric audiologists. Until a network of properly staffed children's hearing assessment centres spans the country,[6] with technologically competent staff and ready access to a full range of techniques for fitting and verifying the performance of suitable hearing aids, it is questionable whether these three requirements are *fully* met. The basis for true diagnosis is rarely present; though there are valid hopes for the future, it is hard at present to justify attempting it, in terms of practical benefit. This has not stopped the term 'diagnosis' being widely misused to refer to the assessment stage where suspected impairments are confirmed or otherwise.

Public health and technique aspects

Late detections are rightly viewed both individually and statistically as serious failures on the part of preventive child health services. Data from screening trials and service monitoring question whether sufficiently early detection of hearing impaired children is being achieved by existing screens on a scale commensurate with their costs. There are five main problems with the screens done by health visitors at 7–9 months, and also with intermediate screens that may exist between 1 and 4 years (although the main problems are less pressing in neonatal and school screens where populations are captive). The five problems are: (i) difficulty in converting free ranging contingency responsive professionals such as health visitors into followers of detailed audiometric procedures[7]; (ii) great difficulties in ensuring coverage above about 95%, with often much lower coverage in deprived areas and among older children; (iii) high risk values for children in problem families not typically reached by the arrangements[8 9]; (iv) a continuous 'background trickle' of detections due to professionals and relatives from birth onwards, on top of which it may be hard to achieve or to show much further yield from the screen; and (v) the high prevalence of fluctuating otitis media with effusion from about 6 months to 6 years of age, complicating any screen with a referral criterion milder than 40 dB hearing loss, and overloading the services with children, of whom only a small minority with permanent hearing loss or persistent otitis media with effusion can or should receive surgical intervention. These five problems conspire to reduce the actual incremental yield of cases from any particular screen.

Typical service review data include the age of detection of known cases, and numbers of cases referred by health visitors; these, plus the presence of multiple screening arrangements can give a false sense of security. Such data are insufficiently analytic to relate the effort and hence the cost of screening to indices of actual health output such as the yield. Some district record systems cannot even demonstrate what proportion of detections are directly due to the screens that occur locally. Equally, claims about sensitivity and specificity of the test procedure under research conditions may not be relevant to a general or particular implementation. For example, the distraction test screen by health visitors at 7–9 months is virtually standard. The *test* can be an excellent and accurate tool in skilled hands,[7] with acceptably high test sensitivity, and it can have positive predictive value over 80%,[3 8] but this is not the main point. In typical screening implementations, the noisy environments, 'rusty' skills, and low coverage lead in effect to much lower sensitivity and positive predictive value for the *system*. Recent studies have documented implementations that are clearly inadequate.[8 10] In the districts with least good services, the median age of confirmation is currently over 2 years—not significantly better than would be expected from that achieved by the 'background trickle' processes involving general practitioners and relatives; only 10–20% will have been detected by 7–8 months. Evidence that many of the difficulties can be overcome with special health visitor training programmes[3 7] may not apply to authorities where population involvement is low or staff recruitment difficult. As only about two to four in every 10 target children found are found by these screens and improvements in their quality, while laudable, can exert only a small effect on the mean age of detection, strategic effort might perhaps be first directed elsewhere.

The crux is whether existence of a screen materially reduces the mean age of detection of permanent hearing losses for the target group in question, compared with absence of that screen. Sensitivity is only one aspect; timing, coverage, and feasibility of rapid follow up are also important. For example, if neonatal screening had a yield of only 50% of the children requiring hearing aids and special habilitative support, this would lead to a materially better result than existing screens at 7–9 months give, because of the very early timing. Davis and Sancho calculated that neonatal screening on an at risk basis could exceed 50% yield, provided that test sensitivity was high. Cross referral of congenital dysmorphologies plus predocumentation of any family history would also need to feed into the screen, adding to presence of the infant in neonatal intensive care, as features defining the risk group.[11] In the event, implementation problems and an apparently lowered prevalence in recent years of impairments in graduates from neonatal intensive care units bring the yield to more like 40–45%. However even this will almost halve the mean age of detection and reduce the median age down to below 1 year when neonatal at risk screening is introduced.

After some false starts with insensitive and non-specific automated behavioural tests such as the auditory response cradle, neonatal at risk screening with sensitive physiological tests has reached the agenda. Child screening versions of tests based on the evoked otoacoustic emission (EOAE)[12] and simplified auditory electrical brainstem response (SABR)[13] show considerable promise of adaptation to the premature population, without excessive loss of sensitivity or specificity. (I do not quote precise figures here for detection age, sensitivity, or specificity because they are always relative to particular populations, and precision in these respects is often spurious in the light of the more influential shortcomings of implementation.) Stevens *et al* suggest that a sensitive screen with EOAE, followed by the more specific contingent sifting by SABR of the failing cases, would be optimal, and this deserves evaluation on very large numbers.[14] McLelland and colleagues in Belfast (R McLelland, *et al*; personal communication) have documented a reduction in median detection age from over 2 years to under 9 months, on the introduction of a neonatal at risk screening programme with auditory brainstem responses, confirming the predicted public health potential of neonatal screening. Although the general picture looks very promising, sufficient trial data have not yet accumulated on neonatal at risk screens to recommend optimal technologies, criteria, and procedures, or to document costs exactly. For congenital sensorineural hearing impairment, with a nominal prevalence rate (including moderate cases) around one per thousand, statistical significance is conspicuously absent from published data, because, to be adequately powerful, trials would need to run for years or to embrace whole nations.

Universal neonatal screening has not yet become credible from the logistical or cost point of view. If current development work were to succeed in making a test short, cheap, and robust enough, universal neonatal screening in 10 years' time would be just conceivable. The main obstacle is the false positives swamping the available assessment facilities, making it impossible to assess all the screen failing children within an acceptably short delay, and undermining the objective of early detection and confirmation! On an at risk basis, assuming that neonatal intensive care facilities are attached to maternity units approaching 5000 births/year, and that agreement is secured for a few simple, but systematic questions to all mothers to be about any family history of deafness, the notional cost per hearing impaired child detected is of the order of £4000 at current prices. This would deteriorate by a factor of about eight for universal screening, and there would be horrendous logistical problems in arranging testing with currently available equipment during the short stay now favoured in maternity wards when births are normal. In relation to the other high costs already incurred neonatally by many of those at risk, and in relation to other costs of rehabilitation and life long support necessary for late detected deaf children, £4000 seems small and highly cost beneficial. However, as the subsequent costs of non-detection fall on departments other than audiology and neonatology (that is, two which would have jointly to set up neonatal screening and the arrangements for assessment), these cost advantages for screening may not immediately win the argument for establishing neonatal at risk screening district by district. Directors of public health with their transdisciplinary perspective would have to take a leading role; the cost effectiveness of neonatal at risk screening should carry considerable force in gaining their support.

By school entry, the screening version of pure tone audiometry ('sweep') is straightforward, and the screening systems employing it are virtually standard. Screening in later childhood is unjustified epidemiologically.[3] In the age range 1–4 years, screening practice in the UK is arbitrary,[3 5] and with the exception of impedance testing for otitis media with effusion there are no proper published studies of optimal method or applications to populations upon which to base a clear view of what should be done in this age range. Spreading recognition of the above five problems of current screens by health visitors with the distraction test, plus the difficulties of treatment and coverage in the intermediate years with existing tests, has led to reappraisal. Screening by test may occur in the future only for the neonatally at risk that it is practicable to test, and universally for school entrants; some other form(s) of surveillance would then have to be delivered for the intervening years. Research and development are required to specify what these alternatives and their performance indicators should be, and to determine how the numerous cases of otitis media with effusion that are non-persistent can best be routed past or out of the system. To deny a dilemma here, on the grounds that general practitioners will in future conduct appropriate surveillance under the new contract, is naive in the instance of hearing, because the problems of coverage, monitoring, training, acoustic environment, and public health control at present seen with health visitors will remain or could even increase. The nature of the work to be done is not only unspecified, but unclear as to desirable and feasible goals. Development of alternatives is urgent, because there are signs that some authorities are already abandoning health visitor distraction test screens in the first year.[15]

Implementation

Deficiencies in the objectives, control, and implementation of screening programmes are widespread, and have diverse causes. Chronic funding difficulties are compounded by problems of recruitment, training, and grading. Justifying the effort on solving these problems presupposes a good public health strategy. Screening programme managers need to harmonise with the directors of public health and with unit general managers to ensure that the goals of a screen are clear and that it is feasible. Where a screen is of long standing, aspects of technique and values of referral criteria may go adrift in the absence of monitoring. On new programmes, an inadequate number or level of staff may have been provided at the outset, or appropriate scientific audiological input may be lacking.[16] Beware the salesman and the accountant who suggest that 'automated' equipment can be run by an unsupported 'button pusher'; developers of equipment rarely achieve that declared goal. In the sharp environment of neonatal intensive care, for example, undergrading of the tester is a recipe for poor cooperation, low coverage, and unreliable results. Commitment to the value of the programme has to be secured, so that virtually all target children will receive the test, and staff sickness or other types of hiatus will not reduce coverage. This is especially important where the screening arrangements are new, and especially with neonatal at risk screening, where the activity is undertaken or hosted by neonatology, a discipline having priorities concerned with life and death, as well as with quality of survival. The wide range of staff whose cooperation is required suggests that published data documenting the effectiveness of screens elsewhere will be necessary, if not sufficient, to secure commitment of all parties. The most crucial step is for neonatologists to agree that they among others 'own' the problem of prelingual deafness.

Listing thus the problems of 'real world' implementation might appear a discouragement from instituting screens that could be made epidemiologically and audiologically valid. However, faith has to be tempered by realism. Creeping, under resourced 'improvements' are all too strong a temptation when the enthusiasm to do good is high but the funding prospects are low. Unfavourable reports of ineffective screens spreading out from under provided and faltering implementations can blight their prospects, however good the idea might be. Programme managers versed in policy, practice, and health service tactics are just as necessary as epidemiologists and bioengineers. The vocabulary of sensitivity, specificity, and positive predictive value was agreed and spread widely 20 years ago, when public health doctors and developers of test procedures recognised one another's arts. They now increasingly have to acknowledge a third art: the managerial art, which is essential for prioritising, establishing, and consistently delivering effective secondary prevention, amid the rival possibilities that compete for attention and funds. A major basis for that art is good research information on what is worth doing. While more such information is, as ever, required, this does not excuse failure to act on the best information currently available.

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The genetics of deafness

'It is certain that whatever diagnostic refinements are employed, it will remain impossible to assign an exact cause of hearing loss in a substantial proportion of deaf persons'. These prophetic words were penned by Dr George Fraser at the conclusion of his survey into the causes of profound childhood deafness in over 3500 patients in 1976.[1] Despite the startling scientific advances which the intervening years have heralded, Dr Fraser's assertion still holds true today. Nowhere is this more pertinent than in a discussion on hereditary deafness because, if an aetiology for deafness cannot be identified, it is impossible to calculate an exact prevalence figure for hereditary deafness. Yet deafness is a common congenital problem with an incidence in the European population of approximately 0·9 per 1000 live births.[2] At least half of the congenital deafness load in a community has been calculated to be due to genetic causes,[3] thus making genetically determined deafness a significant contributor to morbidity in our population.

The spectrum encompassed by hereditary deafness is broad and ranges from simple deafness without other clinical abnormalities (that is, non-syndromic deafness) to genetically determined syndromes wherein deafness is but a feature among a group of clinically recognisable signs that together comprise a syndrome. About 30% of all genetically determined deafness is said to occur in syndromic form. The remaining 70% occurs as non-syndromic forms of deafness and it is to these children that Dr Fraser's comments especially apply, for it is frequently not possible to distinguish deaf children of genetic aetiology from deaf children of environmental aetiology in the absence of other helpful clinical stigmata.

Genetic counselling for deafness

Many of the syndromes that include deafness among their features are inherited in a mendelian manner thus facilitating accurate genetic counselling to affected individuals as to offspring risks, provided the syndrome has been recognised. Among the more familiar such syndromes are Waardenburg's syndrome and Branchio-Oto-Renal syndrome, both of which are inherited as autosomal dominant conditions, and Usher's syndrome, which is inherited in an autosomal recessive fashion. By contrast, genetic counselling in non-syndromic deafness is a much more complex matter. It has been estimated that autosomal recessive forms predominate accounting for 70–85% of genetic non-syndromic deafness.[3] [4] Genes acting in an autosomal dominant manner account for 12–25%[3] of such cases and sex linked genes account for approximately 3%.[1] Although it may be possible to recognise the autosomal dominant and sex linked types on the basis of the inheritance pattern involving other affected family members and counsel accordingly, these individuals will comprise a minority of the genetically deaf population. The vast majority of such cases are due to autosomal recessive genes and the nature of recessive inheritance is, that in a given family, it usually appears in one generation only and, unless there are many affected siblings in that generation, there is no way of knowing whether the deafness in an individual case is genetically or environmentally determined. In these difficult situations the geneticist is forced to rely on empirical risk figures, derived from population surveys of the occurrence of deafness among children of deaf couples, hearing couples, and couples in whom one partner was deaf and the other partner hearing, some such surveys dating from the last century.[5]

A further complication for the geneticist is introduced by the high frequency of marriage between individuals both of whom are deaf. This may lead to a complex genetic situation in which there may be multiple possible causes of deafness in a given pedigree. The combinations of deafness causing genes thus generated can lead to widely varying risks from one deaf couple to the next, risks that may have to be revised after a deaf child is born.

For many monogenic disorders gene tracking or mutation detection by DNA analysis has become an aid to diagnosis and genetic counselling. It is not surprising though that the dramatic advances in identifying gene loci responsible for single gene disorders such as cystic fibrosis[6] have yet to make an impact on non-syndromic forms of deafness. The main obstacle that has retarded the impact of molecular genetics on genetic deafness has been the problem of genetic heterogeneity.

Genetic heterogeneity

Although between 70–85% of non-syndromic genetic deafness is thought to be due to autosomal recessive inheritance,[3] [4] it is known that all autosomal recessive deafness cannot be explained on the basis of mutations at a single gene locus. This conclusion is based on the observation that couples with known autosomal recessive deafness of non-syndromic type usually have children who are all normally hearing.[1] This implies that the deafness in the parents is recessive in origin but involving different gene loci. Estimates vary as to how many mutant loci are capable of causing autosomal recessive deafness. The lowest figure proposed is that of Chung and Brown who suggested that there might be five such loci, based on their observations of the frequency of deaf offspring born to deaf parents.[7] Earlier estimates placed the number of such loci somewhere between 12[4] and 45.[8] As observed by Fraser, there is no means by which these phenotypically similar but genetically distinct forms of deafness can be distinguished.[1] Herein lies the nub of the problem for the genetic counsellor and the explanation for the continuing reliance on empirical risk data. Genetic heterogeneity is not confined to autosomal recessive forms of hereditary deafness for it is thought that a number of different loci may be capable of causing autosomal dominant deafness[4] and there is recent linkage evidence to suggest that not all forms of the rare sex linked deafness involve the same gene locus.[9]

Progress in mapping genes for deafness

In the family linkage strategy, DNA is collected from pedigrees who, indisputably, share the same clinical condition. This DNA is probed using DNA probes of known genetic location with a view to 'mapping' the location of the disease causing gene. In essence one is looking for DNA probes that faithfully coinherit with the disease within the family. When applied to clinical disorders due to a single mutant locus this is a very powerful technique. Its value in genetic deafness is limited by genetic heterogeneity but it has been central to the progress made so far in localising deafness causing genes. In very recent times the genes which cause Waardenburg's syndrome type I[10] and Usher's syndrome type II[11] have been 'mapped' to the long arms of chromosomes 2 and 1 respectively. Now that the responsible genes have been roughly localised, they will in due course be cloned and their protein products become available for comparison with the normal. In this manner we can hope better to understand the pathogenesis of these two forms of genetic deafness in the foreseeable future. Syndromes such as these, which have a clear clinical definition, will continue to be 'mapped' using the linkage approach.

This method will not prove so useful in non-syndromic deafness, however, where families sharing similar inheritance of deafness may not necessarily share the same causative gene. None of the autosomal genes for non-syndromic deafness have yet been cloned but there has been some progress in mapping the X chromosomal genes which may cause non-syndromic deafness. Linkage studies in two separate families had indicated that a locus for deafness could be 'mapped' to the q13–q21 region of the long arm of the X chromosome.[12 13] A further more extensive study, involving several pedigrees has now confirmed this locus.[9] Not all the pedigrees with sex linked deafness can be attributed to this locus, however, and it seems very likely that, even for the very rare sex linked deafness, at least two possible loci may exist.[9]

As the molecular genetics of collagen genes begins to be unravelled an association with deafness is emerging, although the precise nature of that association is at present unclear. What is certain is that a progressive, sensorineural deafness is a common feature of the Stickler-Marshall syndrome.[14] Genetic linkage between the type II procollagen gene (COL2A1) on chromosome 12 and Stickler-Marshall syndrome has been documented in some families with this condition,[15 16] which suggests that mutations in the COL2A1 gene may be responsible for the clinical manifestations of Stickler-Marshall syndrome in the families concerned. Secondly, it is clear that osteogenesis imperfecta type 1 may be linked to either type I collagen subunit gene COL1A1 or COL1A2.[17] However all pedigrees in whom deafness is a feature are linked to the COL1A1 gene on chromosome 17.[18] These data suggest that deafness may result from mutations affecting certain subunits of both types I and II collagen genes but the precise reasons for this observation require further study.

Future progress

For further progress to be made, it is apparent that alternatives to the family linkage approach will have to be employed to surmount the problems posed by genetic heterogeneity. One such strategy would be the study and isolation of genes responsible for non-syndromic deafness in the mouse.[19] By capitalising on the considerable DNA sequence homology between mouse and human genomes, these genes could then be used to search the human genome for genes responsible for deafness. Identification and cloning of such genes with subsequent study of their protein products and the interactions thereof would bring us many new insights into the embryological and pathogenic mechanisms responsible for the complex group of conditions we currently label as non-syndromic deafness. The practical benefits which would accrue from identification of genes capable of causing deafness would be accurate carrier detection tests, more refined genetic counselling with less reliance on empirical risk data and early diagnosis of deafness in at risk individuals based on DNA analysis rather than on less reliable techniques.

Notwithstanding the complexities outlined here, many deaf people and their doctors continue to seek genetic counselling. It is a tribute to generations of past geneticists that their studies are still so pertinent to the modern practice of medical genetics in relation to deafness and a constant reminder of the enormity of the challenges which await solutions in this field.

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Postviral fatigue syndrome

This is a syndrome that may or may not follow what appears to be an acute infectious illness, and may occur in epidemic or sporadic forms consisting of persisting or relapsing 'fatigue' or easy fatiguability of at least six months' duration, for which no other cause is apparent. It is associated with a number of other variable features including mild fever, sore throat, painful lymph nodes, headaches, muscle pain, migratory arthralgia, photophobia, forgetfulness, irritability, concentration difficulties, depression, and sleep disturbance. It has been recognised since the early 1930s and known by a wide variety of names including Iceland disease, Royal Free disease, epidemic neuromyasthenia, myalgic encephalomyelitis, postviral syndrome, and more recently chronic fatigue syndrome.[1]

Although predominantly a disorder of young adults, it has been recognised in children with either an acute or insidious onset. At least 10–15 cases of the sporadic form are seen each year at the Hospital for Sick Children, Great Ormond Street, with lethargy, headache, abdominal pain, and subjective muscular weakness being the most common manifestations. Abnormal physical findings are usually conspicuous by their absence but occasionally pharyngeal injection, tender cervical lymph nodes, and muscle tenderness are present. A proportion of patients have an 'atypical' lymphocytosis, increased plasma creatine phosphokinase activity, circulating immune complexes, minor changes on electroencephalography and electromyelography, increased serum Epstein-Barr and Coxsackie B antibody titres, and VPI antigen in serum. Some workers have demonstrated enteroviral RNA in muscle biopsy material.[2] Although an infective aetiology has been invoked, however, the full nature of the illness remains obscure and is probably a mixture of an initial infective insult followed by or associated with an important psychological component.

The continuing debate as to whether myalgic encephalomyelitis or postviral syndrome is predominantly organic or psychological is unhelpful.[3] [4] As with most childhood illness, it is more useful to pay due consideration to all possible contributory factors including biological, social, and psychological.[5] Elements that have been noted to contribute to the latter include depression, anxiety, school phobia, and family factors such as parental overprotectiveness and over involvement, marital tensions affecting the child, and determination to perceive the problem as exclusively biological.

The polarisation of views concerning the nature of the condition has inevitably affected the approach to management. A number of approaches previously advocated including rest, vitamins, dietary exclusions, immunoglobulin injections, plasmapheresis, and antiviral agents have not clearly been consistently beneficial.[3] At Great Ormond Street, a programme consisting of optimism, support, and rehabilitative strategies is the mainstay of management. Analgesics are used as required. Graded remobilisation is commenced as early as possible. Too rapid mobilisation is likely to lead to early relapse, while continued complete rest can induce a vicious cycle of immobility and,[6] in more severe cases, contractures. The child is encouraged to start with as little as 30 minutes of activity daily divided into two periods, gradually increasing amounts every few days. School return should also be initiated gradually, but definitely, in the same manner. Rarely are antidepressants indicated or of value, but where feelings of guilt, worthlessness, and suicidal ideation are superimposed upon loss of appetite, sleep disturbance, impaired concentration, and psychomotor retardation, then a course of a tricyclic such as amitriptyline 50–100 mg at night for six weeks can be tried as a complement to other treatments.

Family factors that appear to be contributing to maintenance of a disorder should also be tackled. Clearly parental cooperation is required in any remobilisation programme however gradual. When parents express dismay or disagreement, it is helpful to explore their concerns and to explain clearly the rationale, allowing ample time for questions and discussion. Parental support and counselling is necessary throughout the treatment, and family therapy is indicated when there are obvious family problems. The prognosis is variable and most recover completely once the treatment programme is initiated. Only a few children remain, or become, chronic invalids and usually they have parents who are unable or unwilling to accept a comprehensive approach to treatment.

Finally, care should be taken by the profession to avoid unnecessarily burdening children and their parents with a diagnosis of myalgic encephalomyelitis or postviral syndrome. Harris and Taitz have noted that the proffered diagnosis has frequently lead to extensive, unnecessary investigation and inappropriate and untested treatment.[7]

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ORIGINAL ARTICLES

Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance

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Abstract

Evaluation of the sellar area was performed with magnetic resonance imaging in 101 patients (age range 0·8–27 years) with hypopituitarism, isolated diabetes insipidus, hypogonadotrophic hypogonadism, and central precocious puberty. The hypopituitary patients (n=70) included multiple pituitary deficiency (n=23), pituitary deficiency with diabetes insipidus (n=5), and isolated growth hormone deficiency (n=42). The patients with multiple pituitary deficiency showed pathological morphological findings in all cases, with stalk and posterior lobe always involved. The group with associated diabetes insipidus had abnormal stalk in four of five cases and posterior lobe not visible in all cases. Only five of 42 (12%) patients with isolated growth hormone deficiency had abnormalities of the sellar area. In two out of four patients with isolated diabetes insipidus posterior lobe was not seen. All patients with hypogonadotrophic hypogonadism (three with Kallmann's syndrome, one Prader-Willi syndrome, and two idiopathic hypogonadism) appeared normal. In precocious puberty (n=21) the three patients with onset of symptoms before age 2 years exhibited a hypothalamic hamartoma, whereas in the others with onset of puberty between age 2 and 7 the magnetic resonance image was normal in 17 of 18 patients.

The probability of finding a pathological magnetic resonance image was considerably high in our patients with multiple pituitary deficiency, isolated diabetes insipidus, and precocious puberty with very early onset of symptoms. On the contrary, purely functional abnormality is suggested in most patients with isolated growth hormone deficiency, hypogonadotrophic hypogonadism, and precocious puberty with later onset of symptoms.

When a diagnosis of endocrine disorder involving the hypothalamo-pituitary axis is made through functional testing, it is impossible to known whether the defect has an anatomical basis. Magnetic resonance imaging has proved to be the best technique to visualise the sellar and juxtasellar area and it has been used successfully to evaluate children with hypopituitarism, diabetes insipidus, or other disorders in this area.[1–3] In particular the pituitary gland and stalk are clearly seen, even if the association between neuroradiological findings on one hand and type or severity of endocrine alteration on the other has not yet been clarified. In order to investigate this matter further, the sellar area of 101 patients with various endocrine disorders was studied with magnetic resonance.

Patients and methods

We examined 101 patients (56 males and 45 females; age range 0·8–27 years) with the following endocrine disorders: hypopituitarism, isolated diabetes insipidus, hypogonadotrophic hypogonadism, and central precocious puberty.

(1) HYPOPITUITARISM

All patients (n=70) had short stature (below 3rd centile) at time of diagnosis and showed growth hormone deficiency (growth hormone concentration peak <8 μg/l after pharmacological tests and mean growth hormone concentration during night profile <3 μg/l). No patients had a positive history for postnatal head trauma, intracranial tumour, or brain infection. All patients received replacement treatment with pituitary or recombinant human growth hormone. Six patients had stopped taking growth hormone at the time of the examination.

A perinatal history was obtained from the parents or from case records.

These patients were subdivided into the following three groups:

(a) Multiple pituitary deficiency

There were 23 cases (20 males and three females; mean (SD) age 18·3 (4·6) years, range 11·8–27) of whom 17 had adrenocorticotrophic hormone deficiency, 21 thyrotrophin releasing hormone deficiency (protracted or delayed thyroid stimulating hormone response to thyrotrophin releasing hormone with peripheral thyroid deficiency during follow up), and 19 certain gonadotrophin deficiency. All subjects were having appropriate replacement treatment: hydrocortisone acetate for adrenocorticotrophic hormone deficiency, thyroxine for thyroid stimulating hormone deficiency, and human chorionic gonadotrophin and/or testosterone enanthate for gonadotrophin deficiency.

(b) Pituitary deficiency with diabetes insipidus

There were five cases (four males and one female, range 6–15 years). All patients had idiopathic diabetes insipidus and one patient also had thyroid stimulating hormone deficiency. Diabetes insipidus was treated with synthetic antidiuretic hormone, desmopressin (DDAVP, Ferring).

(c) Isolated growth hormone deficiency

There were 42 cases (25 males and 17 females, mean (SD) age 11·6 (3) years, range 5·4–17·9).

(2) ISOLATED DIABETES INSIPIDUS

There were four cases (one male and three females, range 0·8–19 years). All cases suffered from idiopathic diabetes insipidus and were having replacement treatment.

(3) HYPOGONADOTROPHIC HYPOGONADISM

There were six cases (five males and one female, age range 14–16 years) including three patients with Kallmann's syndrome (age 14·8, 15·8, and 16 years), one patient with Prader-Willi syndrome (15·4 years), and two with idiopathic hypogonadotrophic hypogonadism (14 and 15 years). They had not received any previous treatment.

(4) PRECOCIOUS PUBERTY

There were 21 cases (20 females and one male, mean (SD) age 7·5 (3·1) years; age range 0·8–11·2). All cases started puberty before age 7 years and all but two were on treatment with synthetic luteinising hormone releasing hormone analogue (buserelin).

For magnetic resonance a 0·5 T magnet was used in all patients (Philips Gyroscan) with sagittal and coronal images of 2·5 mm slice thickness. Images were obtained with T1 weighted sequences (TR 364 msec, TE 30 msec) and T2 weighted sequences (TR 1500 msec, TE 50/100 msec). The height of the anterior lobe was measured on the sagittal T1 weighted image, using a cursor on the display. A height of less than 2 mm was considered as an indication of small pituitary gland.[4 5] Sedation was necessary in eight patients.

Table 1 Magnetic resonance findings in the 23 patients with multiple pituitary deficiency without diabetes insipidus

No of patients	*Anterior lobe*	*Stalk*	*Posterior lobe*
5	<2 mm	Transected	Ectopic
5	Normal	Transected	Ectopic
1	Normal	Not seen	Ectopic
3	<2 mm	Not seen	Ectopic
1	Normal	Not seen	Not seen
3	<2 mm	Not seen	Not seen
3	Sella partially filled with cerebrospinal fluid		Ectopic
2	Sella filled with cerebrospinal fluid		Not seen

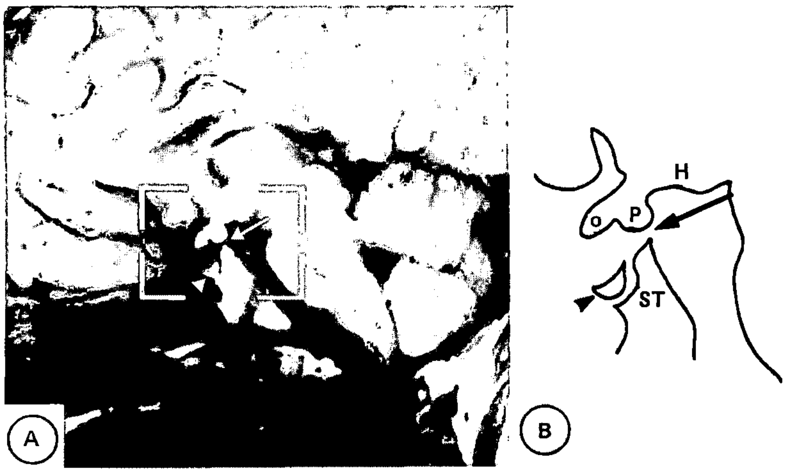

Figure 1 Sagittal magnetic resonance image (A) and line diagram (B) illustrating a hypopituitary patient with multiple deficiency: the stalk is transected (arrow), the bright signal of the posterior lobe (P) is absent in the sella and appears to be present in the median eminence of the hypothalamus. The anterior lobe (arrowhead) is small in height (1·9 mm). Normal appearance of the hypothalamus (H); o: optic chiasm, ST: sella turcica).

Results

(1) HYPOPITUITARISM

All patients with multiple pituitary deficiencies, with or without diabetes insipidus, presented abnormalities of the pituitary or of the stalk.

(a) Multiple pituitary deficiency (table 1)

The stalk was mainly involved: clearly transected in 10 cases (fig 1) and not seen in the remaining 13 cases. The posterior lobe was ectopic at the proximal stump in the 10 patients with transected stalk and in seven other patients. Six patients did not show the characteristic high signal intensity of the posterior lobe. The anterior lobe was abnormal in 16 patients: small in three cases (height of 1·9, 1·5, 1·8 mm) and not seen in the remaining 13 cases; in five of the latter the sellar area was partially or completely filled with cerebrospinal fluid (empty sella). Mean (SD) anterior lobe height in the seven cases with pituitary >2 mm was 3·6 (2·4) mm. There was no correlation between height of the anterior lobe and duration of replacement treatment. Two patients had agenesia of the corpus callosum and one hypogenesia of cerebellar vermis.

In 12 patients (52%) a clear history of adverse perinatal events was found (breech delivery in seven cases, asphyxia in five cases); these subjects did not differ from the others concerning magnetic resonance findings and type of hormonal deficiency. Similarly, the seven subjects with anterior lobe >2 mm (table) did not differ from the others for either the type of hormonal defect or the presence of adverse perinatal events (four out of seven).

(b) Pituitary deficiency with diabetes insipidus (table 2)

In all cases the posterior lobe was not seen. The stalk was not visible in four cases. The patient with growth hormone and thyroid stimulating hormone deficiency had the sella fully filled with cerebrospinal fluid (empty sella). One patient had an anterior lobe of 1·3 mm. No patients had a positive history for adverse perinatal events.

Table 2 Magnetic resonance findings in the five patients with pituitary deficiency and diabetes insipidus

No of patients	*Anterior lobe*	*Stalk*	*Posterior lobe*
3	Normal	Not seen	Not seen
1	<2 mm	Normal	Not seen
1	Sella filled with cerebrospinal fluid		Not seen

Table 3 Magnetic resonance findings in the 42 patients with isolated growth hormone deficiency

No of patients	*Anterior lobe*	*Stalk*	*Posterior lobe*
37	Normal	Normal	Normal
1	<2 mm	Transected	Ectopic
3	<2 mm	Normal	Normal
1	Sella filled with cerebrospinal fluid		Not seen

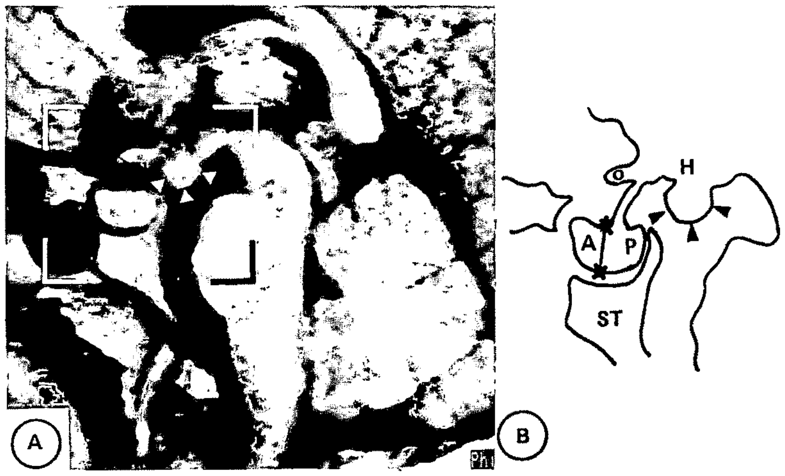

Figure 2 Sagittal image (A) and line diagram (B) of a patient with hypothalamic hamartoma (arrowheads). The stalk, the anterior lobe (A) and posterior lobe (P) are normal. Anterior lobe height (cross) is 8·3 mm.

Table 4 Mean (SD) anterior lobe height (mm) in three groups of patients with anterior lobe height >2 mm

Isolated growth hormone deficiency (n=37)	4·95 (1·03)
Precocious puberty (n=21)	6·25 (1·20)*
Hypogonadotrophic hypogonadism (n=6)	6·55 (1·46)**

*$p<0·025$ compared with isolated growth hormone deficiency.
**$p<0·001$ compared with isolated growth hormone deficiency.

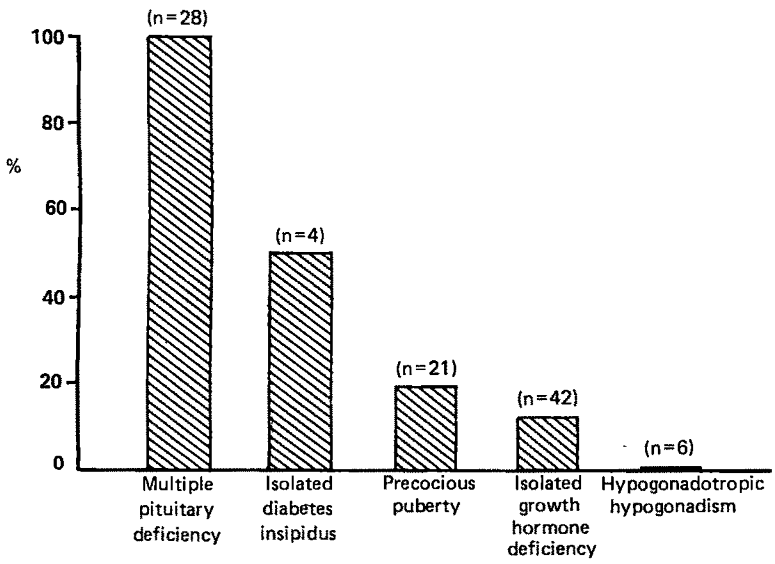

Figure 3 Percentages of pathological magnetic resonance findings in the groups of patients studied.

(c) *Isolated growth hormone deficiency (table 3)*
Only five patients (12%) showed abnormalities of the sellar area. One had an empty sella, one a transected stalk with anterior lobe <2 mm and ectopic posterior lobe, and three had the anterior lobe <2 mm. Twelve patients (29%) had a certain history of adverse perinatal events. Mean (SD) anterior lobe height in the 37 patients with pituitary >2 mm was 4·95 (1·03).

(2) *Isolated diabetes insipidus*
Of the four patients two cases were normal, in one the posterior lobe was not visible, and in one neither the posterior lobe nor the anterior and the stalk were visible.

(3) *Hypogonadotrophic hypogonadism*
All six patients showed a normal hypothalamus and pituitary. Mean (SD) pituitary height was 6·55 (1·46) mm.

(4) *Precocious puberty*
The stalk was faint in only one patient, whereas three patients (14%) had a hypothalamic hamartoma (fig 2); these three patients had the first symptoms before age 2 years.

Mean (SD) pituitary height was 6·25 (1·2) mm. Comparisons between mean pituitary heights in patients with anterior lobe >2 mm are shown in table 4.

Discussion

The examination of the sellar area with this precise, safe technique enabled the observation of a number of morphological features in the pathological conditions studied.

The probability of pathological morphological findings is highest in patients with multiple pituitary deficiency, with or without diabetes insipidus, and lowest in the patients with hypogonadotrophic hypogonadism (fig 3). All our subjects with multiple pituitary deficiency had a pathological magnetic resonance image, with the stalk mainly involved, in accordance with the reports of other authors.[2 6 7] The morphological findings are consistent with suprahypophyseal damage, as suggested by dynamic tests with releasing factors, growth hormone releasing hormone, and thyrotrophin releasing hormone.[8 9] It is interesting to note that all our patients with associated thyroid deficiency, showing abnormalities of the stalk in all cases, had an abnormal thyroid stimulating hormone response to thyrotrophin releasing hormone. These data confirm that deficient thyroid function in hypopituitarism with growth hormone treatment is due to anatomical damage and not to the growth hormone administered.[10]

In our study, there is no clear association between height of the anterior lobe and function of the gland. In particular, unlike Kikuchi *et al*,[6] not all subjects with pathological thyroid stimulating hormone response to thyrotrophin releasing hormone had a 'small-sized' pituitary gland. Furthermore, the patients with isolated growth hormone deficiency (table 4) showed a pituitary height lower than that of the patients with precocious puberty or hypogonadism. As the latter are hypogonadotrophic, the difference in height between the patients with isolated growth hormone deficiency and the other two groups would seem to depend on a different degree of somatotroph activity.

The lack of the posterior lobe visualisation in six patients without diabetes insipidus (table 1), may be related to the normal temporal variation of the intensity of the bright signal, possibly reflecting differing physiological and stress states of patients, as recently described.[11]

A high percentage (88%) of normal magnetic resonance images was found in the subjects with isolated growth hormone deficiency, suggesting purely functional damage.

Unlike findings on computed tomography,[12,13] an empty sella is unusual (eight out of 70, 11%) in our hypopituitary patients examined with magnetic resonance. This diversity might be related to better specificity of magnetic resonance in visualising the sellar content. Our findings are in partial agreement with Surtees *et al*, who reported an association between multiple pituitary deficiency and empty sella, on one hand, and isolated growth hormone deficiency and full sella on the other.

The increased incidence of adverse perinatal events in children with hypopituitarism is well known.[14,15] Recent studies, evaluating the sellar area with computed tomography or magnetic resonance, hypothesise an association between neonatal insult and pituitary anatomical damage. Our data cannot be conclusive on this matter. In fact only 52% of our patients with multiple pituitary deficiency and evident morphological damage have a positive history for adverse perinatal events. This seems to indicate that mechanical or hypoxic perinatal insults cannot be the primary aetiologic factor.

Two out of four patients with isolated diabetes insipidus had a visible posterior lobe. Even if this might not seem in agreement with Fujisawa *et al*,[3] who stated that a normal posterior lobe is equivalent to functional integrity, the possibility of an extra hypophyseal receptor defect as a cause of diabetes insipidus should be considered.[16]

Finally, in the patients with hypogonadatrophic hypogonadism, with or without anosmia, and in 17 out of 18 patients with precocious puberty and onset of symptoms after age 2, magnetic resonance did not identify morphological abnormalities, again indicating a functional defect. On the contrary, in the patients with precocious puberty and very early onset of symptoms (three out of three), a clear abnormality was found (hypothalamic harmartoma), as our previous data provided by computed tomography showed.[17]

In conclusion, magnetic resonance imaging is particularly useful in defining the morphological aspects of the hypothalamo-pituitary region in various endocrine disorders. However, it does not show a constant association between functional endocrine deficiency and neuroradiological abnormalities.

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Increase in urinary growth hormone excretion in puberty

D A Price, G M Addison, E D Herbert

Abstract

During the pubertal years the overnight urinary excretion rate of growth hormone (hGH^{u}) increases to three to four times the prepubertal rate, reaching a peak in girls at 13 years and in boys at 15 years. After puberty the mean rate of overnight hGH^{u} is twice that before puberty.

The amount of growth hormone in the urine is very small compared with that produced by the anterior pituitary, mainly owing to the efficiency of renal tubular reabsorption and hydrolysis.[1] Increased assay sensitivity has allowed the measurement of very low concentrations of human growth hormone in urine (hGH^{u}),[2 3] and good correlation with serum human growth hormone has been reported.[4] During a study of urinary protein excretion in normal children and adolescents we measured overnight rates of hGH^{u} over an age range of 4 to 18 years.

Subjects and methods

Timed overnight samples of urine were collected from 176 schoolgirls and 176 schoolboys who were in good health. There were eight to 12 boys or girls in each age group in the age range 4 to 11 years, and 15 to 22 boys or girls in each age group from 12 years upwards. Urinary volumes were measured and aliquots were stored at −70°C. Aliquots of urine (5 ml) were dialysed against a phosphate buffer (membrane pore size up to 12 000 daltons) for 24 hours at 4°C with two changes of buffer. Human growth hormone concentration was measured by a two step immunoradiometric assay: the first 24 hour incubation was with ^{125}I labelled mouse monoclonal antihuman growth hormone and the second 24 hour incubation with sheep polyclonal antihuman growth hormone antibody coupled to solid phase, both at 4°C. After centrifugation the pellet was washed twice with saline and gamma radiation counted for 10 minutes. Sensitivity was 1·6 pg/tube, intra-assay coefficients of variation were 2·0–8·1% over a range of 4·4–13·6 pg/tube, and interassay coefficients of variation were 6·6–8·4% over a range of 6·9–17·3 pg/tube. No significant change in quality control samples stored at −70°C was observed over two months, the period in which all samples were analysed. Excretion rates were expressed as pg/minute. Statistical comparisons were made using two tailed Student's t tests after logarithmic transformation.

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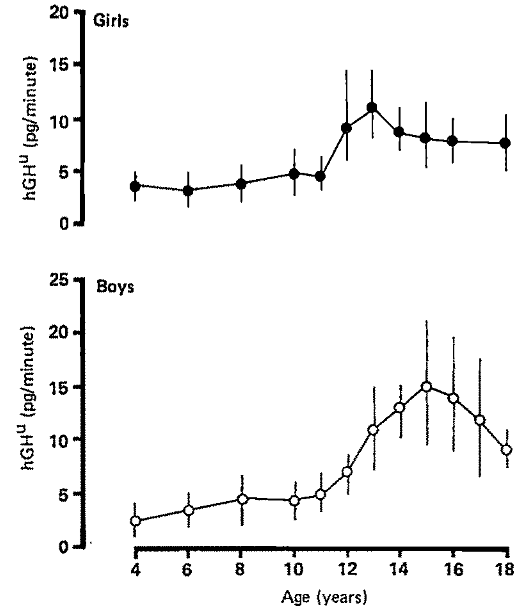

Overnight urinary excretion rates of growth hormone related to age. Results are mean and 95% confidence intervals.

Results

There was no significant change in the overnight rate of hGH^{u} between the ages of 4 and 11 years in girls (mean 4·0 pg/minute, range 0·8–11·4) and in boys (mean 4·0 pg/minute, range 0·6–9·1) (figure). After 11 years of age, excretion rates rose to a peak mean concentration of 10·5 pg/minute (range 4·1–28·1) at 13 years in girls and a peak mean concentration of 15·0 pg/minute (range 2·2–39·0) at 15 years in boys (both peak concentrations significantly greater than the mean levels from 4 to 11 years, $p<0{\cdot}001$). In girls there was a subsequent fall to a plateau between 15 and 18 years at a mean concentration of 7·6 pg/minute (range 2·3–14·2) which was approximately twice that before puberty ($p<0{\cdot}001$). A similar but later fall was seen in boys in whom the mean concentration at 18 years, 9·3 pg/minute (range 5·2–17·4), was twice that in boys 4–11 years ($p<0{\cdot}001$).

Discussion

The amount of human growth hormone measurable in urine is dependent on the secretion rate, the degree of binding to plasma proteins, the glomerular sieving coefficient for the human growth hormone molecule, and tubular reabsorption and subsequent lysosomal hydrolysis. It has been estimated that only 0·01% of human growth hormone production is finally found in urine.[5] However hGH^u measurement seems to have biological meaning in that concentrations are low in hypopituitarism, high in acromegaly,[3] and correlate with serum concentrations in physiological profiles.[4]

In the present study, the increases during pubertal years and the higher concentrations at 18 years compared with prepuberty were significant if analysed with parametric tests after log transformation or with non-parametric (Mann-Whitney) tests ($p<0{\cdot}001$). Although it was not possible to examine pubertal state in this study the significant rise in the pubertal years is likely to reflect increased human growth hormone production during puberty. Using data from 24 hour profiles from Mauras *et al*,[6] there is a fourfold rise in human growth hormone production rates in boys at Tanner stages 4–5 compared with boys at stages 1–2, which is the same relative increase in hGH^u excretion in boys in this study. Furthermore the earlier peak in girls is of interest considering the earlier peak height velocity in female puberty.

Edge *et al* similarly showed an earlier rise in hGH^u in puberty in girls and were able to relate it to breast stage 2 of pubertal development. It is of interest that hGH^u was correlated to growth velocity in girls but not in boys, suggesting growth hormone dependency of the female growth spurt and perhaps testosterone dependency in the male.

Several laboratory methods are now available for the measurement of human growth hormone in urine,[8] and diagnosis of growth hormone deficiency in prepubertal children has been claimed.[9] Further careful studies of normal children before and during puberty are needed to provide a sound comparison for clinical evaluation of growth disorders.

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Assessment of gonadal maturation by evaluation of spermaturia

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Abstract

The urinary excretion of spermatozoa (spermaturia) reflects the achievement of exocrine testis function during male puberty. In order to test the sensitivity and practicability of repetitive urine sampling, we analysed the sediments of 1160 first morning urine specimens obtained on successive days from 129 healthy schoolboys aged 10·1 to 17·8 years for the presence of spermatozoa. The proportion of subjects with sperm positive urines increased from pubic hair stage (PH) 1 (6%) to PH 5 (92%) with a steep rise between PH 2 and 3. Estimated median age of first positive spermaturia ('spermarche') was 14·1 years. While at PH 1 to 4 all positive samples were found within the first five days of collection, at PH 5 cumulative frequency of spermaturia increased up to day 8. We conclude that repetitive morning urine sampling is a useful tool in assessing spermaturia and may be helpful to screen for testicular damage in epidemiological surveys.

The detection of spermatozoa in the urine has been proposed as a quick, non-invasive method to assess the functional state of the maturing gonad and may be useful in screening for spermatogenic damage in male adolescents.[1–6] The evidence derived from longitudinal[2 4 5] and cross sectional[3] studies that spermaturia is a discontinuous phenomenon seems, however, to limit its value as a routine screening procedure. In those earlier reports either a single 24 hour urine[2 5] or variable numbers of morning urine specimens[4 6] were analysed. Considering the intermittent appearance of spermaturia, which probably occurs as a urethral wash out phenomenon after involuntary or masturbatory sperm emission,[7] the probability of urinary sperm excretion should rise according to the number of specimens collected. No systematic investigations have been performed, however, in study populations of adequate size over extended periods of time so far. Therefore, we attempted to determine the sensitivity and practicability of repetitive morning urine collections in a group of 129 healthy peripubertal boys, and to relate spermaturia to their state of sexual maturation.

Table 1 Age distribution of the 129 boys under study. Age ranged from 10·1 to 17·8 (median 12·8) years

	Age (years)						
	10	*11*	*12*	*13*	*14*	*15*	*16–17*
No of boys	14	26	31	14	20	18	6

Subjects and methods

One hundred and twenty nine healthy boys from five secondary schools in the city of Heidelberg agreed to participate in the study. The distribution of age and stages of puberty are given in tables 1 and 2. The children and their parents were informed that the purpose of the study was to evaluate normal sexual maturation by clinical assessment and urinary hormone excretion; however, they were not aware that spermaturia was investigated.

The boys were requested to collect their first morning void for two consecutive weeks from Monday to Friday respectively. In case of night time micturition they were advised to collect the first nocturnal urine. The specimens were brought to school in 100 ml plastic vessels and collected daily by one of the investigators. The bottles contained 3 ml of a 0·7% saponin solution in 0·4% aqueous formalin. The urine was stored at 4°C and analysed within 10 days after collection.

Urine analysis was performed according to the method described by Hirsch *et al.*[3] In brief, a 10 ml aliquot of the well shaken urine was centrifuged at 1800 *g* for 15 minutes. The pellet was resuspended in 0·5 ml of the supernatant after decantation. The resuspended sediment was examined microscopically. Forty visual fields were checked at a magnification of ×400 for the presence of spermatozoa. The same observer (JM) investigated all specimens. A specimen was considered sperm positive if one or more spermatozoa were detected.

At the end of the first week of urine collection, a clinical examination of the pubertal status was performed by a single observer (JM). Genital and pubic hair stage was recorded according to Tanner.[8] The volume of each testicle was estimated by use of a Prader orchidometer, and the mean volume of the two testes was calculated.

ANALYSIS OF DATA

As not all boys delivered complete series of 10

Table 2 Distribution of Tanner stages of puberty (n=129). PH=pubic hair stage, G=genital stage

	PH1	*G1*	*PH2*	*G2*	*PH3*	*G3*	*PH4*	*G4*	*PH5*	*G5*
No of boys	34	41	45	27	16	14	17	14	17	33

Table 3 Distribution of number of collected urines

No of urine specimens collected	*No (%) of subjects*
4	2 (1·6)
5	6 (4·7)
6	2 (1·6)
8	5 (3·8)
9	10 (7·7)
10	104 (80·6)
	129 (100·0)

morning urine specimens (table 3), the cumulative probability to remain sperm negative was calculated by use of the Kaplan-Meier life table analysis.[9] The subjects who dropped out of the study before spermaturia was detected were classified as lost to follow up at the last day of collection and treated as censored data. Spermaturia rates were estimated stratified by age, pubertal stage, and testicular volume.

The median age at spermarche, defined as the age at which spermaturia can be demonstrated in 50% of a given population, was estimated by probit analysis.[10] In this procedure, the percentage of subjects exhibiting spermaturia are recorded at the successive age stages. To this percentage distribution a probit transformation is applied, and a regression line fitted to the probit values. Thus it is possible to calculate the median and variance of age at spermarche, assuming a Gaussian distribution of the timing of the event in the population.

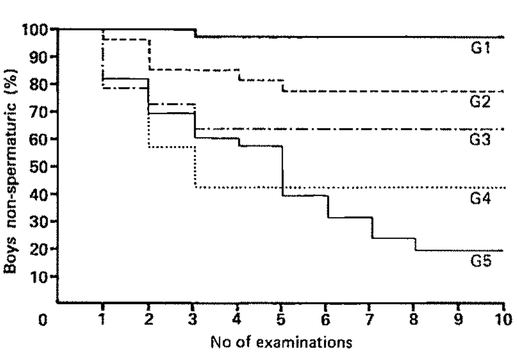

Figure 1 Kaplan-Meier estimation of probability to remain sperm negative in up to 10 consecutive morning urine samples, stratified by Tanner's genital (G) stage.

All calculations were performed by use of the respective procedures supplied in the SAS software package.[11]

Results

As shown in table 3, the overall participation rate in the study was very high. Almost 90% of the boys collected nine or 10 morning urines. A total of 1120 specimens was analysed.

The Kaplan-Meier analysis of all patients' probability to remain sperm free with increasing numbers of examinations is shown in fig 1, stratified by Tanner's genital (G) stage. The proportion of sperm positive subjects increased with the state of genital maturity. After 10 urine collections, less than 20% of the boys in G5 had not exhibited spermaturia in any specimen, whereas in G1 spermatozoa were only found in one out of 40 boys. In presence of stages G1 to G4, no new sperm positive individuals were detected beyond day 5, whereas in G5 the cumulative frequency of spermaturia gradually increased up to day 8.

Similar analyses were performed according to the other maturational parameters under study. A survey of the probability of spermaturia as calculated by Kaplan-Meier estimation is given for age, pubertal stages, and testicular volume in fig 2. Age and testicular volume were subdivided into five classes. No subject was found sperm positive below 11 years of age; in the upper age groups, only about two thirds of the boys exhibited spermaturia. When related to pubic hair (PH) stage, a steep rise of the sperm positive fraction was seen between PH2 and PH3, with more than 90% being positive at PH5. The most discriminative parameter was testicular volume; when the mean testicular size exceeded 20 ml, 93·5% of the subjects excreted urinary sperm.

The probit analysis for the estimation of the age at spermarche is depicted in fig 3. The median age at spermarche was calculated as 14·1 years, with a 95% confidence interval of 13·5 to 14·9 years.

We also performed a quantitative analysis of spermaturia. The number of positive morning urine specimens per subject ranged from one to nine. A wide variation of sperm concentration (one to 458 spermatozoa/40 visual fields) was noted. In the sperm positive individuals no

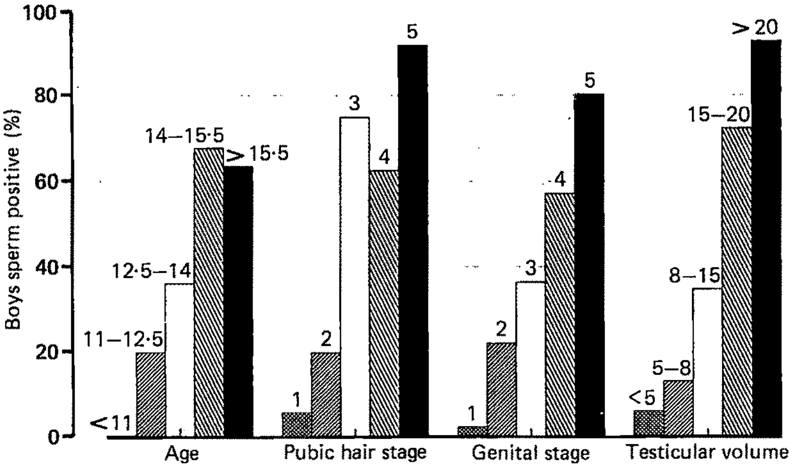

Figure 2 Overall cumulative probability of spermaturia according to age, Tanner stages for pubic hair (1–5) and genitals (1–5), and testicular volume (ml) (n=129).

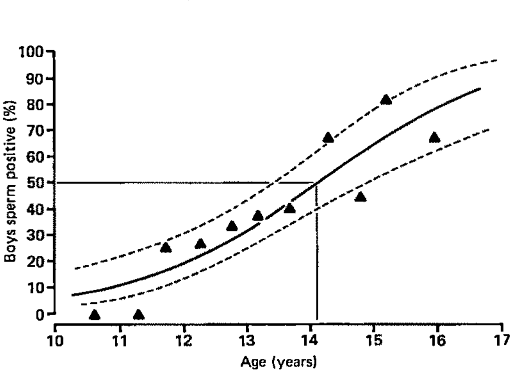

Figure 3 Probit analysis of median age at spermarche. Age was grouped in six month intervals. Triangles mark unsmoothed percentages of sperm positive individuals per age group. Full line indicates smoothed sigmoid probability curve, dotted lines 95% confidence intervals.

significant correlation was found between the number of spermatozoa per 40 visual fields and age (r=0·09, p=0·52) or testicular volume (r=0·23, p=0·12). The correlations were not improved when the sperm count was related to urinary creatinine concentration to account for the varying dilution of the morning urines.

Discussion

The primary target of our study was to evaluate how regularly spermaturia can be picked up in healthy boys by the consecutive collection of 10 morning urines. In contrast to earlier studies[3 4] the good compliance of the study participants allowed us to calculate overall probability rates from appropriate numbers of boys at all stages of puberty.

Our data demonstrate that spermaturia is better predicted by the clinical stage of puberty than by chronological age. The most powerful criterion to be sperm positive was a mean testicular volume of greater than 20 ml, but also in Tanner PH stage 5 more than 90% of the boys exhibited spermaturia (fig 2). Thus it is evident that spermaturia is detectable in the large majority of sexually mature subjects within a 10 day period of observation. Detailed analysis of cumulative spermaturia rates according to the number of investigated urines indicates that, however, once spermarche has occurred, spermaturia is a more regular event during early and mid puberty than in grown up individuals, where the first spermatozoa sometimes were not detected before the eighth day of collection (fig 1). This finding confirms an earlier suggestion by Hirsch *et al* who, analysing a maximum of five consecutive morning urine specimens, found a more slowly rising cumulative probability of spermaturia in 16 year olds compared with younger boys.[3] We assume that this difference may reflect changes from predominantly spontaneous nocturnal sperm emission towards rather intermittent masturbatory ejaculations in late puberty.

The high sperm detection rate in mature boys with the sampling protocol used in this study also indicates that a 10 day repetitive morning urine collection is more suitable to identify reliably postspermarcheal subjects than a 24 hour or a short term morning urine sampling regime as proposed in earlier reports.[2 3 5]

Despite the high sensitivity of our sampling technique it probably does not allow quantitative estimations of sperm production during puberty. In early studies of biopsy specimens a gradual increase of the density of mature spermatozoa in the tubular lumen during adolescence has been demonstrated,[12] and immediate postejaculatory urinary sperm concentrations correlated with ejaculate sperm counts.[7] Thus one might expect that the sperm number observed in the urine sediment should increase with advancing puberty. Yet no such correlation was found, possibly due to previous voiding between ejaculation and urine collection, variable urine volume and concentration, or other factors.

The median 'age at spermarche' observed in this cross sectional study was 14·1 years. In relation to pubertal stage, the 50% mark was between PH 2 and 3, although in a few cases spermaturia was found even in clinically prepubertal boys. Despite methodological and ethnic differences these results compare well with the findings of Richardson and Short who found a median age at spermarche of 13·3 years,[2] Hirsch *et al* (14·5 years),[3] and Nielsen *et al* (13·4 years).[5] It is also noteworthy that the median age at spermarche found in these studies corresponds to the age at first conscious ejaculation as evaluated by interviews.[13]

In summary, repetitive assessment of spermaturia is a sensitive, ethically acceptable, noninvasive procedure to determine the state of spermatogenic activity in pubertal subjects. The method cannot replace detailed quantitative sperm analysis, but may be used as a qualitative screening test to investigate potential damage to the maturing testis. It appears also suitable for epidemiological investigations in precocious or delayed puberty, for patients having chemotherapy or irradiation treatment, or for those with other chronic diseases potentially adversely affecting the gonads. Results of such studies can be analysed using the methods and be compared with the normal data presented in this study.

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Indices of intact serum parathyroid hormone and renal excretion of calcium, phosphate, and magnesium

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Abstract

Up to date reference ranges were established for fasting renal excretion of calcium, phosphorus, and magnesium on 101 healthy children aged 2–15 years. A normal range for intact parathyroid hormone was also measured.

The indices of calcium and magnesium excretion showed no correlation with age or sex so that a common range for all children could be established. The 97th centile values for urinary calcium:creatinine and magnesium:creatinine ratios were 0·69 mmol:mmol and 1·05 mmol:mmol respectively. The calculated tubular maximum for phosphate/litre of glomerular filtrate ($TmPO_4$/GFR) showed no correlation with age with a geometric mean value of 1·67 mmol/l.

The normal range for intact serum parathyroid hormone for the age group was 11–35 ng/l, which is lower than the adult normal range using the same assay. There was an inverse correlation between $TmPO_4$/GFR and intact parathyroid hormone in this group of normal children.

Investigation of disorders of mineral metabolism in children require reference to recognised normal ranges. Measurements of the renal handling of calcium, phosphorus, and magnesium are important in the elucidation of such disorders. Assessment of renal calcium handling is necessary in determining the contribution made by the kidney to hypocalcaemia and hypercalcaemia. In addition hypercalciuria is recognised not only as a risk factor for renal calculi but may also be a factor in a variety of other symptoms related to the urinary tract in children.[1]

Measurement of the renal tubular handling of phosphorus is necessary in the investigation of hypophosphataemia, which may be due to a primary renal tubular defect or secondary to a disturbance of parathyroid hormone function. Similarly, investigation of hypomagnesaemia in children, although rare, relies on measurement of urinary magnesium excretion to distinguish between a selective defect in intestinal absorption or a renal tubular leak. An accurate measurement of parathyroid hormone can also be of help in the investigation of such disorders.

Data available from different populations or different decades may not be applicable because of racial differences and changes in diet that occur with time.[2] Normal values for parathyroid hormone concentration in serum have also changed because of the development of sensitive assays for the intact molecule in recent years. It was with the aim of producing reliable up to date reference ranges in British children that this study was undertaken.

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Patients and methods

Urine samples were collected from 101 healthy children aged 2 to 15 years who had been fasted for at least 10 hours overnight before day case surgery. These samples were the second urine sample passed in the morning—that is, the first specimen after the overnight urine had been passed. A venous blood sample was collected at the same time with minimal venous stasis. The children were all ambulant before the samples being obtained and none was taking drugs known to affect the urinary excretion of calcium, phosphorus, or magnesium. The study was approved by the Leeds Eastern Health Authority ethical committee.

Plasma and urine calcium and magnesium were analysed by atomic absorption spectrophotometry. Creatinine was analysed by a kinetic Jaffé method and phosphate using ammonium molybdate in both urine and serum with a Beckmann Astra 8. Sufficient blood was simultaneously obtained from 78 children, stored at 4°C until clotted, and subsequently serum stored at −20°C for later measurement of parathyroid hormone. Intact parathyroid hormone was measured using a two site immunoradiometric assay (PTH-Allegro).

The following indices were calculated. Fasting calcium and magnesium excretions were expressed as the ratio of their concentrations to the creatinine concentration in urine. In addition they were expressed as fasting calcium and magnesium excretion indices, which allow for variation in renal function, calculated by multiplying the ratio of urinary calcium or magnesium to creatinine concentration by the plasma creatinine to give values in µmol/litre of glomerular filtrate.[3]

The renal tubular handling of phosphorus was expressed as the tubular maximum reabsorption rate of phosphate per litre of glomerular filtrate ($TmPO_4$/GFR)[4] using the computer calculated formula based on Bijvoet's data.[5] As the data were not normally distributed centiles were calculated for the indices of calcium and magnesium excretion and serum parathyroid hormone concentrations. The data for $TmPO_4$/GFR were expressed as geometric means and 95% tolerance limits for different age groups. Correlations were performed after the data had been logarithmically transformed to produce normal distributions.

Results

All the children studied had normal values for plasma calcium, magnesium, phosphate, and creatinine. The calculated indices of fasting calcium and magnesium excretion showed no association with age or sex and demonstrated an approximately log normal distribution (fig 1). The results of both sexes were therefore pooled and centiles calculated for the age group studied (table 1). A strong positive correlation was seen between the calcium:creatinine ratio and the calcium excretion index in this group of children with normal renal function (r=0·97, p<0·001). A similar correlation exists between the magnesium:creatinine ratio and the magnesium excretion index. A positive correlation was also observed between the calcium:creatinine ratio and the magnesium:creatinine ratio (r=0·3, p=0·004).

The values for $TmPO_4/GFR$ demonstrated no correlation with age. No difference in values was observed between the boys and girls. The data has been expressed as geometric means and 95% tolerance limits for different age groups (table 2). As there was no correlation with age in this group of children, however, the geometric mean and 95% tolerance limits for the whole group are also given. A similar range is seen if centiles are calculated.

The values for intact parathyroid hormone also showed no association with age or sex so that a common normal range was calculated for the age group 2–15 years, which has again been represented as centiles (table 3). The association between parathyroid hormone and $TmPO_4/GFR$ was examined and a significant inverse correlation was found (r=−0·31, p=0·04) in this population of normal children (fig 2). There was no significant correlation seen between parathyroid hormone and the calcium:creatinine ratio (r=−0·03, p=0·86) or the magnesium:creatinine ratio (r=−0·21, p=0·17).

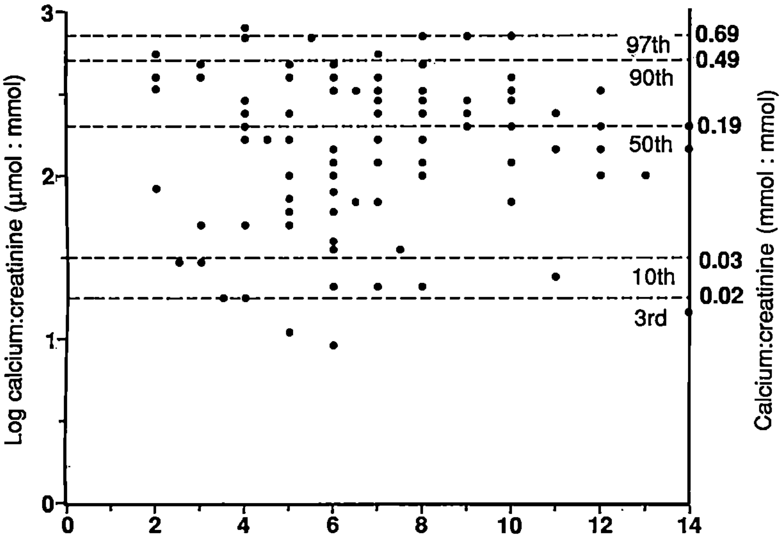

Figure 1 Values for calcium:creatinine ratio on 101 children aged 2–15 years depicted on a logarithmic scale indicating the centiles.

Table 2 Normal values for $TmPO_4/GFR$ by age

Age (years)	*Geometric mean (mmol/l)*	*Tolerance limits (mmol/l)*
2–3·9	1·70	1·04–2·79
4–5·9	1·66	1·05–2·60
6–7·9	1·72	1·26–2·35
8–9·9	1·59	1·1 –2·31
10–11·9	1·72	1·15–2·58
12–14·9	1·57	1·18–2·09
2–15	1·67	1·15–2·44

Table 3 Normal values for intact parathyroid hormone

Centile	*Parathyroid hormone (ng/l)*
3	11·0
10	12·0
50	18·5
90	29·0
97	35·0

Discussion

Our study presents normal values for urinary calcium and magnesium excretion in British children and in addition values for the tubular maximum reabsorption threshold of phosphate and the concentration of intact parathyroid hormone in serum for which data in this group have not previously been available.

There have been several other studies that have quoted normal ranges for urinary calcium and magnesium excretion in children,[6–9] but the values presented have varied making it difficult to define what is abnormal. Calcium and magnesium excretions can be assessed either by a 24 hour urine collection or more simply by the ratio to creatinine in a single urine sample. It is generally accepted that the upper limit of normal for 24 hour urine calcium is 0·1 mmol/kg/day.[6] A previous study on British children investigated in the 1970s demonstrated a good correlation between the 24 hour urinary calcium and the calcium:creatinine ratio of the second morning urine obtained in the fasting state, the latter demonstrating the least variation.[6] The upper limit of normal for fasting calcium: creatinine ratio in that study was 0·74 mmol: mmol. This result differs from several other published studies. Stapleton *et al* obtained fasting urine samples on 48 healthy American children aged 3 to 16 years after five days on a diet

Table 1 Centiles for indices of fasting calcium and magnesium excretion

Centile	*Calcium:creatinine (mmol:mmol)*	*Magnesium:creatinine (mmol:mmol)*	*Calcium excretion index (µmol/l glomerular filtrate)*	*Magnesium excretion index (µmol/l glomerular filtrate)*
3	0·02	0·18	1·0	5·5
10	0·03	0·22	1·4	10·4
50	0·19	0·41	9·1	18·4
90	0·49	0·69	21·9	32·2
97	0·69	1·05	34·8	49·3

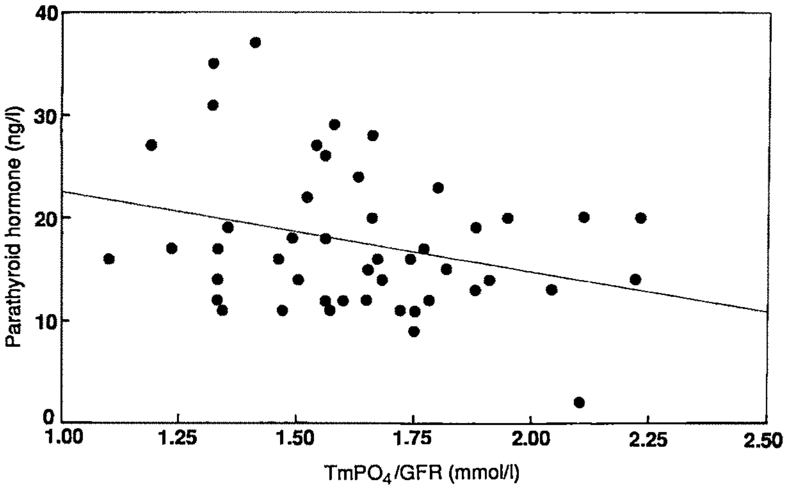

Figure 2 Correlation between the tubular maximum reabsorption rate of phosphate per litre of glomerular filtrate ($TmPO_4/GFR$) and intact molecule parathyroid hormone.

that avoided milk products and vitamins.[7] The upper limit, calculated by adding the arithmetic mean plus two standard deviations, was 0·59 mmol:mmol. Moore *et al*, who collected random urine samples on 273 predominantly black American children aged 3 months to 16 years on unrestricted diet, quote an upper limit of 0·51 mmol:mmol again based on an arithmetic mean plus two standard deviations.[8] Kruse *et al* collected fasting urine samples on 564 German schoolchildren aged 6–18 years who were on an unrestricted diet.[9] Their data was log transformed and the results expressed as centiles giving a 97th centile value of 0·49 mmol:mmol. Some of the variation can be accounted for by racial or dietary differences and by the fact that one of the studies was undertaken in non-fasting conditions.[8] In addition, some of the quoted upper results are based on arithmetic means and standard deviations which are an incorrect method of representing data that is not normally distributed. This would have had the effect of producing lower upper limits. The 97th centile value in our study of 0·69 mmol:mmol is close to the value of 0·74 mmol:mmol obtained by Ghazali and Barratt[6] so it would appear that values of this magnitude can be applied to British children but may not be applicable to other population groups. As in other studies no association with age and sex was demonstrated for calcium and magnesium:creatinine ratios so that a common normal range can be used.

There have been few previous studies that have reported urine magnesium:creatinine ratios in children. Ghazali and Barratt reported an upper limit of normal of 1·95 mmol:mmol in 29 children studied in the fasting state,[6] whereas Moore *et al*,[8] using a larger sample of 273 children, report a much lower non-fasting value of 0·54 mmol:mmol.[8] However, both these studies have presented values based on arithmetic means. Our study using fasting morning urines gives a 97th centile value of 1·05 mmol:mmol. The same value is obtained if the data is log transformed and the upper 95% tolerance limit calculated. The only other apparent explanation why the upper limit of normal for magnesium: creatinine ratios in our children should differ from those in the other two studies is because of possible differences in the diets of the children studied.

The calcium and magnesium excretion indices are calculated values that allow for renal function permitting comparison of individuals with different glomerular filtration rates. It is often used as the preferred index in adult studies such as the investigation of familial hypocalciuric hypercalcaemia. Our study has shown a very strong correlation between these indices and the calcium and magnesium:creatinine ratios, which is not surprising as the variation in plasma creatinine concentration in normal children of the age group was small. Thus although in a group of children with normal renal function the excretion indices offer no advantage, the normal values may be of use in the investigation of children with impaired renal function.

It is important to note that in the calculation of the excretion index for calcium or magnesium the plasma creatinine has been expressed in μmol/l. However when calculating clearances or tubular maximums the value of plasma creatinine must be converted to mmol/l as urinary creatinine is expressed in these units.

It has been recognised for a long time that the fractional excretion of phosphate and its inverse, the tubular reabsorption of phosphate, are not sensitive measures of renal phosphate handling. The tubular maximum reabsorption threshold for phosphate which corrects for variation in glomerular filtration rate has been regarded as the most suitable index. A nomogram was constructed by Walton and Bijvoet from which a knowledge of the serum phosphate and the tubular reabsorption of phosphate would allow calculation of the tubular maximum ($TmPO_4/GFR$).[10] This has been used to calculate normal ranges for $TmPO_4/GFR$ in children[11] and infants under 6 months.[12] Two equations have been derived from the nomogram of Walton and Bijvoet which can be solved by a programmable calculator or computer to simplify calculation of $TmPO_4/GFR$.[5]

There are some differences seen between our study and other published data on $TmPO_4/GFR$ in children.[11] [12] Kruse *et al* demonstrated an inverse correlation between $TmPO_4/GFR$ and age which was not seen in our study.[11] This may be due to our smaller sample particularly the low numbers in our sample who were postpubertal where the main fall in $TmPO_4/GFR$ was seen in their study. Certainly our values are higher than the accepted normal range in adults which is 0·8–1·35 mmol/l.[10] We have presented our data for different ages but because of the lack of correlation with age we have also presented a common range which may be easier to use in practice. The other main difference seen between our study and that of Kruse *et al* is that our mean values for $TmPO_4/GFR$ are significantly lower than theirs, the geometric mean value in our study of 1·67 mmol/l being equivalent to their mean value seen at age 13 to 14 years. This could be accounted for by racial or dietary differences emphasising the importance of having reference values appropriate for the particular population being studied. Unlike their study we did demonstrate a significant inverse correlation between $TmPO_4/GFR$ and parathyroid hormone which probably reflects the fact that intact molecule parathyroid hormone is a more sensitive assay of parathyroid hormone activity than the predominantly C-terminal assay they employed.

Until recently there have been difficulties in reliably measuring serum parathyroid hormone. Earlier assays that relied on antisera to discrete parts of the hormone, such as the N-terminal, C-terminal, and the mid-molecular region, were not able to distinguish reliably between normals and abnormals. In addition studies have shown an appreciable disparity between circulating concentrations of parathyroid hormone measured by these older immunoassays and biologically active parathyroid hormone measured by a cytochemical bioassay.[13] New assays have been developed that specifically recognise intact parathyroid hormone, which is the principal bioactive form.[14] These are sensitive and have the ability to distinguish between normals, patients with primary hyperparathyroidism, and patients with non-parathyroid hypercalcaemia. They are also the most appropriate assay for individuals with chronic renal failure. Although there are data available for adults using these assays,[14 15] there is little information on values in normal children. The adult normal range using the immunoradiometric assay as used in this study is 10–65 ng/l (Allegro, Nichols Institute). Kruse *et al* report a normal range of 14–55 ng/l from a control group that included children but they quoted a common range that included people with an age range of 5–43 years without distinguishing between the results obtained from the adults and children.[16] Our results using the immunoradiometric assay show that the normal range for intact parathyroid hormone is lower in children. The values obtained using this assay, although lower than those found using fragment assays, are probably still higher than those found in sensitive bioassays.

There have been several previous studies using older parathyroid hormone assays in normal children with differing results. Clayton *et al* found values of parathyroid hormone to be lower in children under the age of 6 years but adult values were found by the age of 8 years.[17] Arnaud *et al* found higher than adult values in children under 6 years but lower values in the 6 to 12 year age group. Stark *et al*, using an assay specific for the C-terminal end of the molecule found values in children up to the age of 16 years to be lower than adults.[19] It is difficult, however, to compare these studies because of the different parathyroid hormone assays used. Our results resemble those of Stark *et al* in that the parathyroid hormone concentrations using the intact molecule assay were lower than adult values throughout the 2 to 15 year age group studied. The correlation of $TmPO_4/GFR$ and intact molecule parathyroid hormone suggests that the former is a reliable parameter of parathyroid function in normal children. The relatively small differences in parathyroid function in children and adults are not likely to be solely responsible for the differences seen in tubular phosphate reabsorption. There may be other influences acting on tubular phosphate reabsorption in children to account for this.

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Helicobacter pylori and associated duodenal ulcer

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Abstract

Twenty three children with coexistent duodenal ulcer and *Helicobacter pylori* infection were treated with either two weeks of amoxycillin (25 mg/kg/day) in addition to six weeks of cimetidine, or cimetidine alone. Endoscopy with antral and duodenal biopsies for urease test, microaerophilic culture, and histological studies were performed at entry, six weeks, 12 weeks, and at six months. Children with persistent *H pylori* infection at six weeks were given a further two weeks' course of amoxycillin. *H pylori* persisted in all children not receiving amoxycillin treatment but cleared in six of the 13 children (46%) treated with amoxycillin. With failure of *H pylori* clearance at six months, only two out of six (33%) ulcers had healed and 50% of patients had experienced ulcer recurrence. In contrast, when *H pylori* remained cleared all ulcers healed and no ulcer recurred. Persistent *H pylori* infection was associated with persistent gastritis and duodenitis despite endoscopic evidence of ulcer healing. Detection and eradication of *H pylori* deserves particular attention in the routine management of duodenal ulceration in children.

The association between the presence of *Helicobacter pylori* in antral mucosa and histological gastritis has now been well established both in adults[1 2] and children.[3 4] It has also been shown in adults that *H pylori* infection plays an important part in the healing and relapse of duodenal ulcer.[5] Similar studies are, however, lacking in children and the above association between *H pylori* infection and duodenal ulceration in the paediatric population still requires clarification. This report documents a prospective study to evaluate the clinical, endoscopic, microbiological, and histological features of duodenal ulcer associated with *H pylori* in children after amoxycillin treatment.

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Patients and methods

Twenty three children (mean age 11·2 years, range 4–16) diagnosed endoscopically to have duodenal ulcer with coexistent isolation of *H pylori* from the gastric and/or duodenal mucosa were entered into the study. There were 15 boys and eight girls. Ten children had a history of upper gastrointestinal bleeding, and in 13 upper endoscopy had been undertaken for recurrent upper abdominal pain of three or more months' duration. Patients in whom gastric or duodenal biopsy was contraindicated and those who had recently completed an antibiotic course before endoscopy were excluded from the study. Written informed consent was obtained from parents before inclusion.

ENDOSCOPY AND BIOPSY

Endoscopic examinations were performed using a paediatric forward viewing gastroscope (Olympus GIF XP or GIF P2). Acute duodenal ulcers with no endoscopic evidence of chronicity (that is, deep lesions with fold convergency and bulb deformity) were included in the study but superficial mucosal erosions and ulceration secondary to steroids, stress, etc, were excluded. Two gastric mucosal biopsy specimens were taken from the antrum at 1–2 cm from the pylorus. The first specimen was divided into two portions. One portion was immediately ground in the endoscopy room for the rapid urease test using 1 ml of freshly prepared 10% urea solution,[6] and the other was despatched immediately for microbiological smear and culture. The second biopsy specimen was fixed in formol saline for histological section. Two mucosal biopsy specimens were also taken from the duodenal cap adjacent to the ulcer and were processed in a similar manner to the gastric biopsy specimens.

HISTOLOGY

Histological sections of the specimens were stained with haematoxylin and eosin for grading of gastritis and duodenitis, and with Warthin-Starry stain to demonstrate the bacteria. Antral gastritis was graded according to the criteria of Whitehead *et al*,[7] depending on the presence or absence of polymorphonuclear leucocytes and the intensity of inflammatory cell infiltration. Active chronic gastritis (polymorphonuclear leucocytes present) was graded with scores from 0–3 (absent, mild, moderate, severe). A score of 0–3 was also assigned for duodenitis according to the classification described by Wyatt *et al* (table 1).[8]

MICROBIOLOGY

A portion of the specimen was examined by Gram stain and it was then inoculated after grinding onto a brain heart infusion agar with vancomycin, nalidixic acid, and amphotericin B within three hours of collection. The plates were incubated at 37°C in a microaerophilic environment and examined at the fourth and seventh day before being discarded.

All laboratory investigations were conducted

Table 1 Grading of duodenitis

Grade	*Degree of duodenitis*	*Histological features*
0	Normal	Normal duodenal architecture
1	Insignificant duodenitis	Architectural changes only with no definite increase in inflammatory cells
2	Chronic duodenitis	Definite increase in mononuclear cells in the lamina propria with evidence of epithelial degeneration
3	Active duodenitis	Changes of chronic duodenitis plus presence of intraepithelial neutrophils

without prior knowledge of endoscopy findings, treatment regimen or *H pylori* state. A patient was defined as *H pylori* positive if the bacteria were identified either by histological examination or culture, and *H pylori* negative if the bacteria were not detected.

TREATMENT REGIMEN

A decision regarding treatment was made immediately after endoscopy according to the result of the urease test. *H pylori* was assumed to be present when a biopsy specimen showed a positive urease test as indicated by a definite colour change from yellow to pink within five minutes. Patients with a positive result were then randomly assigned to receive either two weeks of amoxycillin (25 mg/kg/day in three divided doses) in addition to a six week therapeutic course of cimetidine (20 mg/kg/day in three divided doses), or cimetidine alone. All patients with a positive urease test had *H pylori* infection confirmed subsequently on histological examination or culture, and no patient was removed from the study with a false positive urease result.

Endoscopy with antral and duodenal biopsies for urease test, microaerophilic culture, and histological studies were repeated immediately after six weeks' treatment and again at 12 weeks. All patients with *H pylori* detected again at six weeks received a further two week course of amoxycillin. In addition, patients with unhealed or partially healed ulcers were given further six week courses of cimetidine until complete healing was achieved. Maintenance treatment with nocturnal dosage of cimetidine, 10 mg/kg, was given only to patients who required more than one therapeutic course of cimetidine for complete ulcer healing. Follow up endoscopy and biopsy were repeated again at six months after entry.

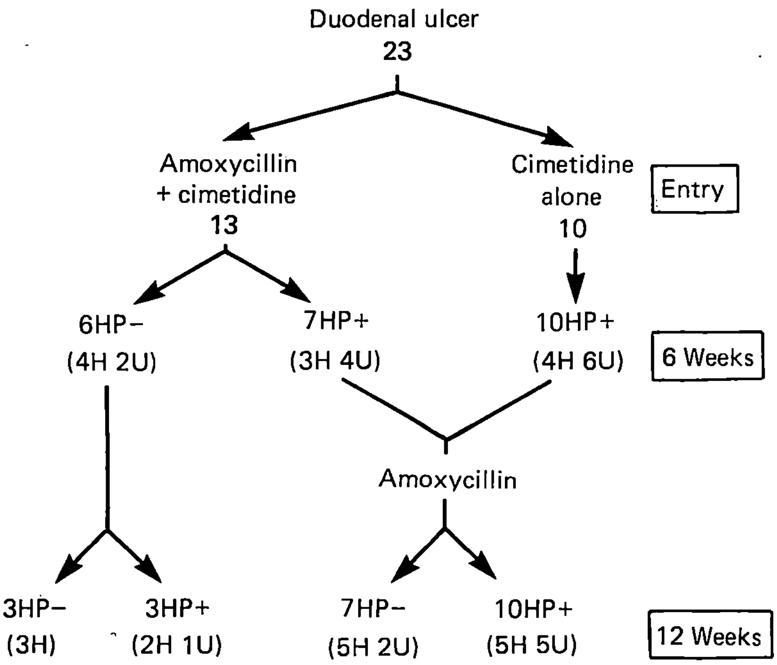

Figure 1 Treatment regimen, H pylori state, and ulcer healing (H=ulcer healed, U=ulcer unhealed, HP− =H pylori negative, HP+ =H pylori positive).

STATISTICAL ANALYSIS

Data analyses were performed using the χ^2 test with Yates's correction and the Wilcoxon test, p values of $<0\cdot05$ were considered to be significant.

Results

EFFICACY OF TREATMENT FOR H PYLORI ERADICATION

All 23 children completed 12 weeks of treatment, although three were lost to follow up at six months. For the first six weeks of treatment, 13 children received two weeks of amoxycillin with cimetidine, whereas the remaining 10 children were given cimetidine alone (fig 1). Endoscopy and biopsy after six weeks treatment showed that six of 13 children (46%) who received amoxycillin became *H pylori* negative. In contrast, all 10 children not receiving amoxycillin remained positive ($p<0\cdot02$).

The 17 children who remained positive at the end of six weeks were given a further two week course of amoxycillin. Seven of these 17 (41%) became negative and 10 remained positive for *H pylori* on endoscopy at 12 weeks. Of six children with initial clearance at six weeks, three remained negative and three were found to have a relapse of *H pylori* infection.

Twenty children were available for follow up at six months. Four of 10 children with clearance of *H pylori* at 12 weeks had a relapse of infection and only six remained negative after initial clearance. Of 10 children with *H pylori* infection at 12 weeks, only one child had spontaneous clearance of *H pylori* and nine remained positive. Six of these nine children were persistently infected throughout the study period without clearance of *H pylori*.

ULCER HEALING AND SYMPTOMATIC RELIEF (TABLE 2)

After the first six week treatment period, four of six children who were then negative had healed their ulcers whereas only seven of 17 (41%) children still positive had endoscopic ulcer healing ($p>0\cdot2$). On repeat endoscopy at 12 weeks, ulcer healing had taken place in eight of 10 children in the negative group compared with only seven of 13 children (54%) in the positive group ($p>0\cdot15$). On follow up at six months all six children who remained negative after initial

Table 2 Clinical, endoscopic, and histological changes with clearance of H pylori after amoxycillin treatment

	At entry	*H pylori at 6 weeks*		*H pylori at 12 weeks*		*H pylori at 6 months*	
		Negative	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*
No of children	23	6	17	10	13	7	13
Ulcer symptoms present	17	1	8	2	8*	0	6*
Endoscopic findings:							
Nodular antritis	11	1	7	2	4	0	5
Ulcer healed	0	4	7	8	7	7	8
Ulcer unhealed	23	2	10	2	6 (1)	0	5 (3)
Histological findings:							
Active chronic gastritis	23	2	16*	3	12*	3	13*
Significant duodenitis (grade 2 and 3)	14	3	10	1	7*	1	8*

Numbers in parentheses denote ulcer recurrence.
*Significant difference (p<0·05) between positive and negative groups.

clearance had healed ulcers. In contrast, ulcers had healed in only two of six children with persistent *H pylori* infection throughout the study period (p<0·02).

Only one child who was negative for *H pylori* at six weeks had persistent abdominal pain compared with eight who were positive (p>0·15). At 12 weeks, two of 10 children in the negative group had residual abdominal pain compared with eight of 13 children in the positive group (p<0·05).

ULCER AND SYMPTOM RECURRENCE (TABLE 3)

An 11 year old boy with persistent *H pylori* infection was found to have early asymptomatic relapse of ulcer at 12 weeks. Three more children in the positive group were also found to have ulcer recurrence on endoscopy at six months, two of whom had complained of recurrent abdominal pain. None of the six children who remained negative at six months after initial clearance had developed a recurrent ulcer. In contrast, all three children with ulcer recurrence at six months had persistent *H pylori* infection throughout the study period (p<0·05). All seven children in the group negative for *H pylori* at six months were symptom free whereas six of 13 children in the positive group still had residual pain (p=0·03).

SIDE EFFECTS OF TREATMENT

Five of the 23 children developed side effects on amoxycillin treatment: three with protracted diarrhoea and two with skin eruptions. These symptoms subsided spontaneously after cessation of treatment. There were no side effects observed related to cimetidine treatment.

HISTOLOGICAL GASTRITIS AND DUODENITIS

H pylori was detected in 66 of 89 available antral biopsy specimens, with 64 (97%) having histological evidence of active chronic gastritis. In the remaining two without histological gastritis, coexistent duodenal biopsy specimens showed active duodenitis with *H pylori* being detected in one. Eradication of *H pylori* was associated with a significant improvement in the severity of histological gastritis (fig 2). The mean score for polymorphonuclear leucocytes for active gastritis in the clearance group at 12 weeks decreased from 1·50 before treatment to 0·30 after *H pylori* eradication (p<0·01). In contrast, the score in the persistently infected group fell only from 1·54 to 1·23 (p>0·15). Relapse of infection was associated with a significant worsening of active gastritis.

Table 3 Ulcer recurrence and H pylori infection

	H pylori at 12 weeks		*H pylori at 6 months*	
	Negative	*Positive*	*Negative*	*Positive*
Ulcer recurrence	0	1	0	3 (3)
No recurrence	10	12	7*	10 (3)

Numbers in parentheses denote persistent *H pylori* infection throughout study period.
*Six remained negative after initial eradication.

The grading of duodenitis also correlated significantly with *H pylori* infection and histological active gastritis but did not correlate well with endoscopic ulcer healing (fig 3). The mean duodenitis score in the negative group at 12 weeks decreased from 1·80 before treatment to 0·60 after *H pylori* eradication (p<0·01). In contrast, the duodenitis score in the positive group only fell from 1·77 to 1·54 (p>0·3).

Active duodenitis (intraepithelial neutrophils present) was found in 21 of 89 (24%) duodenal biopsy specimens and gastric metaplasia on 26 occasions (29%) of which 17 were associated with active duodenitis. The presence of *H pylori* in duodenal mucosa was detected in 10 biopsy specimens, all showing histological evidence of active duodenitis. Furthermore, the presence of *H pylori* in duodenal mucosa was confined to areas of gastric metaplasia.

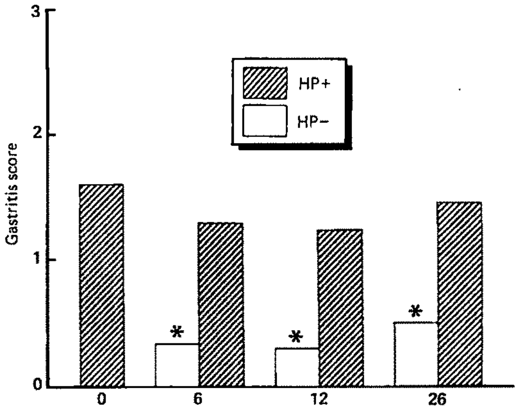

*Figure 2 Effect of clearance, of H pylori on gastritis score (number of polymorphonuclear leucocytes present). (HP−=H pylori negative, HP+=H pylori positive.) *p<0·01.*

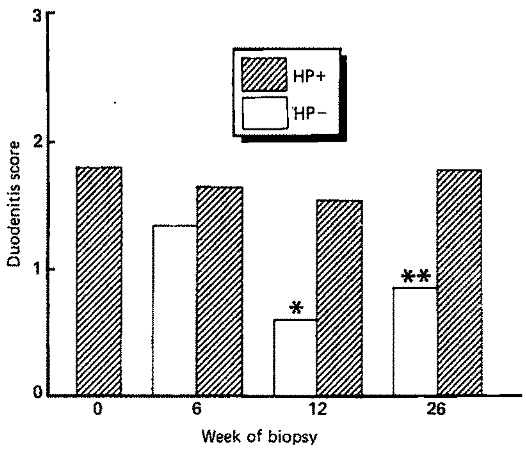

Figure 3 Effect of clearance of H pylori on duodenitis score. (HP− = H pylori negative, HP+ = H pylori positive.) *$p<0·01$, **$p<0·05$.

Discussion

With the more frequent application of flexible upper endoscopy and hence more accurate diagnosis of lesions in the upper gastrointestinal tract,[9] the detection of duodenal ulcer in children has increased appreciably in our practice in recent years.[10] Although the use of H_2 receptor antagonists has resulted in improved ulcer healing rates, recurrence of ulceration frequently occurs in over one third of patients.[11, 12] Marshall *et al* suggested that the presence of *H pylori* infection was the most important aetiological factor in the pathogenesis of duodenal ulcer diathesis, as persistent *H pylori* infection had been shown to be associated with significantly lower ulcer healing rates and a greater likelihood of ulcer recurrence.[5] Similar studies of *H pylori* associated duodenal ulcer in children and its treatment have not been reported previously. It has, however, been shown that in children with refractory duodenal ulcer, a six week course of amoxycillin achieved complete ulcer healing.[13] This supports the hypothesis that microbial infection might also play an important part in the pathophysiology of peptic ulcer disease in childhood. In this study, all children who remained cleared of *H pylori* after initial eradication had healed ulcers at six months without recurrent ulceration. In contrast, with failure of eradication of *H pylori* only 33% of ulcers healed ($p<0·02$) and 50% recurred ($p<0·05$) during the six month period. Children in the group negative for *H pylori* also experienced significantly less abdominal pain when compared with the persistently infected group.

As clearance of *H pylori* has only been observed with antimicrobial treatment,[2, 13–15] and spontaneous remission of *H pylori* infection rarely occurred with use of H_2 receptor antagonists alone,[5] a combination of bactericidal and ulcer healing agents appears promising for treatment of duodenal ulceration in children.[16] The use of amoxycillin to eradicate *H pylori* infection has been disappointing in this study as fewer than half of the patients responded and relapse of infection was common. Furthermore, side effects including protracted diarrhoea and skin rash were troublesome. Although Oderda *et al* have reported the effective use of amoxycillin (50 mg/kg/day, twice the standard dosage) plus tinidazole for six weeks in eradication of *H pylori* infection without mention of any side effects,[17] it is unlikely that children in our locality can tolerate such a dose. It has recently been shown in adults that a combination of colloidal bismuth subcitrate and tinidazole was much more effective in healing ulcers and preventing recurrence than cimetidine alone.[5] The use of bismuth preparations in children is, however, less desirable because of its possible neurotoxicity and arthrotoxicity in the growing child, and hence better therapeutic agents must still be sought.

The presence of *H pylori* in the gastric antrum was strongly associated with active chronic gastritis and this is in accordance with most reports in adults.[1, 2, 13–15] The severity of active gastritis correlated only with *H pylori* state and significantly improved with eradication of infection. There is little understanding of the strong correlation between *H pylori* associated gastritis and the presence of inflammatory infiltrates in the duodenum. It has been shown in this study that when *H pylori* was present in the duodenum, this was always associated with active duodenitis.[18, 19] According to the hypothesis that duodenitis represents a part of the pathophysiological spectrum of duodenal ulcer diathesis,[8, 18] persistent duodenitis associated with the persistence of *H pylori* infection after endoscopic ulcer healing might well be of importance in the pathogenesis of duodenal ulcer diathesis and recurrence.

Gastric metaplasia was also found in duodenal mucosa in children in this study, although the frequency of 29·2% was lower than most reported series in adults.[7, 18, 20] It is interesting to note that the presence of *H pylori* in the duodenum was invariably confined to areas of gastric metaplasia and was always associated with active duodenitis.[8, 19] As it has also been shown that *H pylori* infection was associated with hypergastrinaemia and increased serum pepsinogen I concentrations,[17, 21] it may be postulated that *H pylori* infection can act synergistically with acidpepsin induced gastric metaplasia to produce active duodenitis and mucosal damage which may culminate in ulceration.

In summary, our results document that persistent *H pylori* infection is associated with persistence of gastritis and duodenitis despite endoscopic evidence of ulcer healing. Significantly more patients in the persistently infected group had unhealed ulcers with residual symptoms and ulcer recurrence. We support the proposals of Marshall *et al*[5] and recommend that detection and eradication of *H pylori* deserves particular attention in the routine management of duodenal ulceration in childhood.

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See related paper on p 1278.

Long term survival with trisomy 18

Most children with trisomy 18 survive for only a short period. Approximately 70% survive the first month, 50% the first two months, and 10% the first year. A few survive into later childhood and survival into the 20s has been known. Van Dyke and Allen (*Pediatrics* 1990;85:753–9) describe six children who lived for more than a year. One was still alive at the age of 6 years but the other five had died at between 13 and 29 months of either heart disease or pneumonia. The main physical management problems in long term survivors are feeding problems, infection, congenital heart disease, and scoliosis due to hemivertebrae. The authors emphasise the importance of sympathetic psychosocial management for the family unit, the recognition of reactive and preparatory grief in the family, and the provision of a coordinated team approach.

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Severe hypertension after liver transplantation in α_1 antitrypsin deficiency

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Abstract

Five children with α_1 antitrypsin deficiency and terminal liver disease received liver grafts; all five became hypertensive and four developed hypertensive encephalopathy. There was evidence of renal disease preoperatively and renal biopsy specimens showed variable glomerulonephritic histology with IgA nephropathy in one, mesangial-proliferative changes in two, and mesangiocapillary glomerulonephritis type I in two. Four hypertensive episodes were preceded by a fall in creatinine clearance. The association of glomerulonephritis with α_1 antitrypsin deficiency in children is more common than has been recognised. Affected patients are prone to severe hypertension of probable renal origin after liver transplantation and the renal lesion may affect long term prognosis.

Orthotopic liver transplantation has been used to treat a wide range of potentially lethal liver disorders. In children long term survival rates have gradually improved,[1,2] but postoperative complications remain frequent and severe, including graft loss and multiorgan failure. Postoperative hypertension is common and usually ascribed to cyclosporin toxicity.[3–6] Among 91 children who received liver transplants in Cambridge between December 1983 and August 1989 postoperative hypertension occurred in 28 (30%) overall. In children with biliary atresia (n=40) the incidence was 22·5% (n=9) and in children with α_1 antitrypsin deficiency (n=14) 71·5% (n=10).

Deficiency of α_1 antitrypsin is associated with liver and lung disease. There is also an infrequently reported association with membranoproliferative glomerulonephritis (new terminology: mesangiocapillary glomerulonephritis type I) usually demonstrated only at necropsy.[7–9] The true frequency of renal lesions in these patients is unknown. We report here five children with α_1 antitrypsin who received liver grafts and had perioperative renal biopsies.

Patients and methods

Five patients with α_1 antitrypsin and genotype PiZZ in end stage liver failure received orthotopic liver grafts at Addenbrooke's Hospital, Cambridge, between December 1983 and August 1989. Routine preoperative renal function tests included regular urine analysis and plasma creatinine, urea, and electrolyte estimations. In addition urinary protein loss, creatinine clearance, and glomerular filtration rate were measured in some patients (table). Renal biopsy specimens were obtained during liver transplantation in cases 1, 2, and 4, four weeks postoperatively in case 3, and before the transplant in case 5. Postoperative monitoring included daily 24 hour urine collections for urinary electrolytes and creatinine clearance for the first three to seven days. Serial creatinine clearance measurements are shown in figs 1–5. This method for calculating glomerular filtration rate is accurate in the presence of normal glomerular function but tends to give falsely high values when glomerular function is poor.[10] Relative changes in glomerular filtration rate rather than absolute values are therefore reported and only those plasma creatinine and blood pressure measurements that demonstrated a change from the previous measurement or were abnormal are shown. All blood pressure measurements were taken by the Dinamap non-invasive monitor and the maximum mean arterial pressure of the day was recorded. We have reported only episodes of severe hypertension (mean arterial pressure greater than the 95th centile for age[11]) which required treatment with antihypertensive agents for at least 48 hours. If there was evidence of associated fluid overload this is indicated in the case descriptions.

The following immunosuppressive regimen was used: intravenous methylprednisolone 10 mg/kg preoperatively and 2 mg/kg/day intravenously or orally from day 1 postoperatively, azathioprine 1·5 mg/kg/day intravenously or orally from day 1, and cyclosporin 1 mg/kg intravenously twice a day (infusion over six hours) on day 2, increased to 2 mg/kg twice a

Preoperative highest recorded blood pressure measurements and results of hepatic and renal function tests. Normal values are given in parentheses

Case No	*Albumin (30–51 g/l)*	*Prothrombin time (12–16 sec)*	*Bilirubin (2–17 µmol/l)*	*C3 (60–180 mg/100 ml)*	*Plasma creatinine (27–62 µmol/l)*	*Creatinine clearance (90–120 ml/min)*	*Urinary findings*	*Blood pressure (mmHg)*
1	33	19	46	50	43	317·0	Proteinuria, haematuria	120/80
2	29	20	46	55	61	46·2	Proteinuria 0·3 g/day, haematuria	120/70
3	28	18	37	31	67	—	Proteinuria, haematuria	146/80
4	31	16	23	62	38	66·3	Proteinuria 1·8 g/day, haematuria	120/70
5	20	12	26	57	55	86·0	Proteinuria 2·6 g/day	120/80

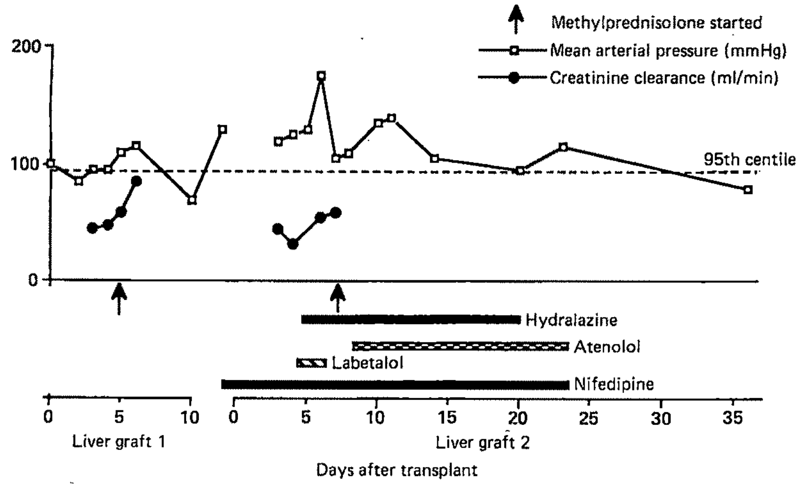

Figure 1 Case 1 (age 3·9 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

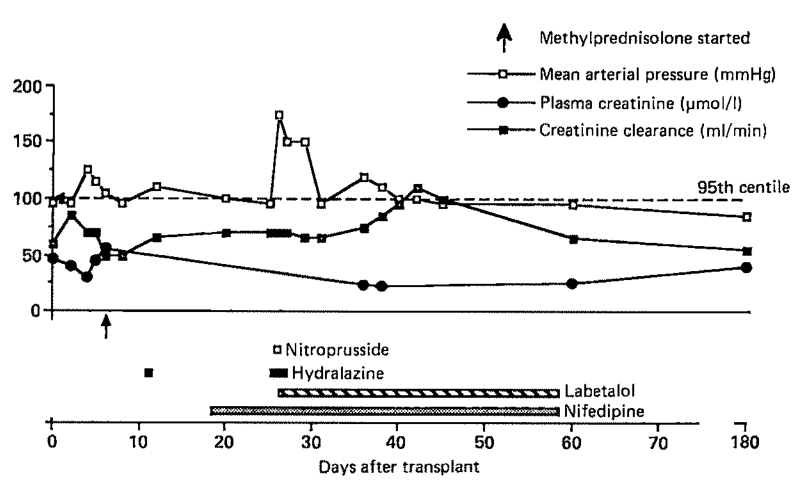

Figure 2 Case 2 (age 5·7 years): plasma creatinine, serial creatinine clearance, blood pressure, and drugs given after transplant.

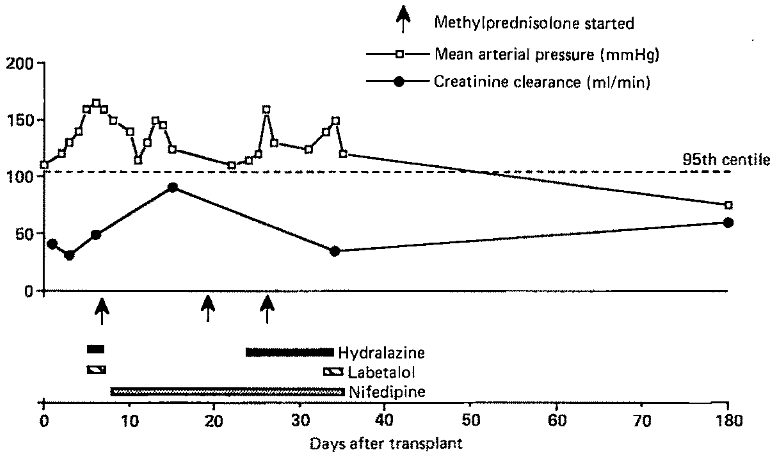

Figure 3 Case 3 (age 8·2 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

day from day 3. Trough whole blood cyclosporin concentrations were measured daily by the selective monoclonal antibody based radioimmunoassay (Cyclotrak–SP, Incstar). Episodes of acute rejection were treated with a three day course of intravenous methylprednisolone based on weight (125 mg/day less than 10 kg, 250 mg/day 10–20 kg, and 500 mg/day greater than 20 kg). For persistent and severe rejection a 10 day course of antithymocyte globulin was given.

Results

Salient clinical and laboratory details are shown in the table and figures.

CASE 1

This girl received a liver graft at the age of 3·9 years. Two days before transplantation she was noted to have macroscopic haematuria but she was normotensive. A renal ultrasound scan was normal. An operative renal biopsy specimen showed mild mesangial matriceal increase, thickening of the capilliary walls, and intense diffuse staining for IgA, IgG, IgM, C3, and C1q consistent with a diagnosis of IgA nephropathy. Staining for α_1 antitrypsin was negative. On electron microscopy scattered mesangial and paramesangial deposits were identified. On the fifth postoperative day she suffered acute graft rejection unresponsive to methylprednisolone and antithymocyte globulin progressing to liver failure. Before retransplantation she developed severe gastrointestinal bleeding and became hypertensive possibly due to fluid overload. She received a reduced liver graft on the 13th postoperative day. Four days later she became severely hypertensive. She was agitated, confused, and tremulous but there were no seizures. Intravenous cyclosporin was stopped, although plasma concentrations were within the therapeutic range. Despite vigorous treatment with antihypertensive agents her blood pressure could not be controlled effectively. A further episode of acute rejection occurred on the seventh postoperative day, this time successfully treated with methylprednisolone. This was associated with a further rise in blood pressure. Antihypertensives were withdrawn after four weeks. Four months after transplantation she is well and no further episodes of haematuria have been documented.

CASE 2

This boy received a liver graft at the age of 5·7 years. At 5 years of age he had had recurrent episodes of abdominal pain, macroscopic haematuria, and proteinuria. His blood pressure was normal. A renal ultrasound scan demonstrated no abnormality. An operative renal biopsy specimen showed a diffuse glomerulonephritis of mesangiocapillary type I, all the glomeruli showing mesangial hypercellularity and matriceal increase. On the fifth postoperative day he developed acute rejection that was successfully controlled with methylprednisolone. He lost huge volumes of ascitic fluid from the peritoneal drains, however, reaching a maximum of eight litres per day and requiring massive replacement with clotting factors and human albumin. From the 12th day the ascitic fluid was recycled untreated and from the 22nd to the 27th day recycled as an ultrafiltrate. This procedure was well tolerated with normal cardiovascular and respiratory function but with shifts in sodium balance. On day 26 his oral fluid intake was low, his urine output diminished, and the urea rose, indicating early prerenal failure and he had a hypertensive crisis with a maximum blood pressure of

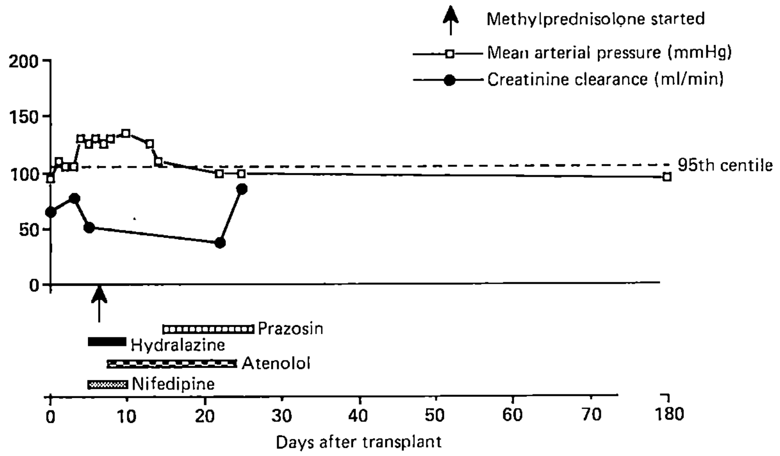

Figure 4 Case 4 (age 8·5 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

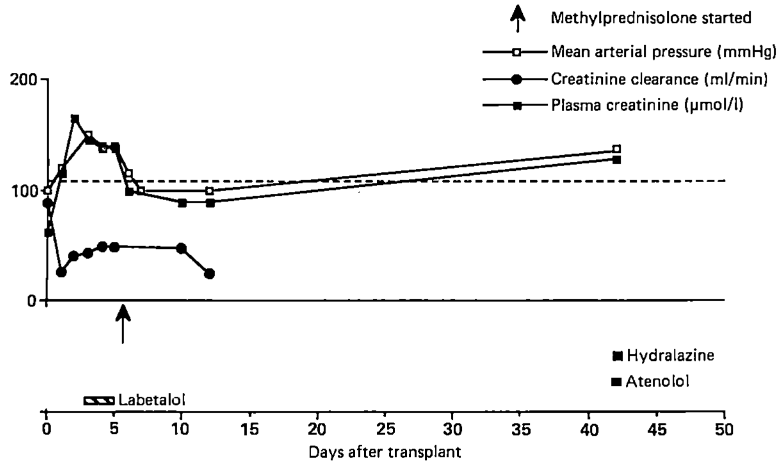

Figure 5 Case 5 (age 14·6 years): plasma creatinine, serial creatinine clearance, blood pressure, and drugs given after transplant.

200/150 mm Hg. Despite aggressive treatment with antihypertensive agents he had several grand mal convulsions and episodes of unresponsiveness. Intravenous cyclosporin was stopped, although concentrations were within the therapeutic range. A computed tomogram and examination of his cerebrospinal fluid were normal. By day 31 the blood pressure was controlled but on day 36 he required a laparotomy for biliary peritonitis and postoperatively the blood pressure was again raised and there was evidence of renal impairment with oliguria and a rise in plasma creatinine. Three days postoperatively he had a urinary tract infection associated with haematuria and proteinuria. All antihypertensive agents were stopped 3·5 months after transplantation and urinary protein losses were normal after six months.

CASE 3

This girl received a liver graft at the age of 8·2 years. Three months before transplantation she had deteriorated rapidly with weight loss and increasing ascites requiring regular albumin transfusion. Two episodes of haematuria and proteinuria were observed one year and one week before transplantation and her blood pressure was slightly raised (145/80 mm Hg) a few days before transplantation. A renal ultrasound scan was normal. Postoperatively she developed severe hypertension. On day 5 here blood pressure reached 200/120 mm Hg and she became unresponsive. A computed tomogram of her head and her cerebrospinal fluid were normal. She developed macroscopic haematuria. Intravenous cyclosporin was stopped, although drug concentrations were within the therapeutic range. On day 6 she became more responsive but had five grand mal convulsions. By day 10 her blood pressure was under control and neurologically she had fully recovered. She then developed severe acute rejection that required three courses of methylprednisolone and one course of antithymocyte globulin for control. Steroid treatment on all three occasions was associated with an increase in blood pressure, haematuria, and heavy proteinuria. Four weeks after transplantation a renal biopsy specimen showed mesangialproliferative glomerulonephritis with mesangial hypercellularity and diffuse obliteration of epithelial cell foot processes. Staining for IgA was negative and for α_1 antitrypsin positive. The glomerular filtration rate measured at this time was normal (104 ml/min). All antihypertensive agents were stopped six weeks after transplantation. The creatinine clearance was normal seven weeks after transplantation and proteinuria fell to 0·4 g/24 hours at four months.

CASE 4

This boy received a liver graft at the age of 8·5 years. At 7 years he had had his first episode of haematuria and proteinuria but was normotensive. Four months before transplantation he developed severe ascites requiring paracentesis and albumin transfusions. An intraoperative renal biopsy specimen showed mesangiocapillary glomerulonephritis type I with an increase in mesangial cells, mesangial interpositioning, and thickening of the basement membrane. On immunofluorescence there was diffuse, granular deposition of IgM, IgG, IgA, C3, and C1q on glomerular capillary walls. Postoperatively he developed asymptomatic hypertension on day 5 that worsened when high dose steroid treatment was started on day 6 for acute rejection. Cyclosporin concentrations were within the therapeutic range. From day 14 his blood pressure was controlled on oral antihypertensive agents. The creatinine clearance fell to 37 ml/min on day 22 but then increased to normal. Four months after transplantation he was well with a normal blood pressure on treatment with prazosin.

CASE 5

This girl received a liver graft at the age of 14·6 years. At 8 years a severe haemorrhage from oesophageal varices had required an emergency portocaval shunt. At 12 years she had peritonitis caused by *Escherichia coli* and proteinuria was detected. Four weeks before transplantation a renal biopsy specimen taken at another hospital showed a mild mesangialproliferative glomerulonephritis. A renal ultrasound scan demonstrated enlarged kidneys but she was normotensive. The intraoperative course was complicated by bleeding requiring six litres of blood replacement. Over the next 36 hours she continued to bleed, requiring a further six litres of blood, and developed renal impairment with a rising plasma creatinine and urea. On day 3 she became hypertensive and on day 4 developed hypertensive encephalopathy with coma. At that time she had not received any cyclosporin. By day 6 her blood pressure was controlled and she had fully recovered neurologically. On the same day she developed acute rejection and high dose steroid treatment was started during which her blood pressure remained stable. Six weeks after transplantation she had several grand mal convulsions at home. She was found to be hypertensive (blood pressure 170/100 mm Hg) and in renal failure with a plasma creatinine concentration of 128 μmol/l and a urea of 19 mmol/l. She recovered neurologically after vigorous antihypertensive treatment. Unfortunately she died two years later from sepsis and in renal failure while awaiting retransplantation for chronic rejection. Necropsy was not performed.

Discussion

The outcome of liver transplantation has improved progressively in recent years.[2] Most deaths occur within one month of the operation, the major problems including surgical complications, graft rejection, liver infarction, and infection.[3] Some degree of postoperative hypertension is common,[3–5] but it is rarely reported as severe or life threatening. Non-renal causes of hypertension include insufficiently controlled pain or anxiety, water and sodium overload, and drug side effects. Cyclosporin toxicity in particular has been associated with hypertension,[6] which probably results from direct and indirect vasoconstrictive effects on the afferent glomerular arteriole.[12] The most favoured hypothesis suggests that cyclosporin augments thromboxane A_2, which produces renal vasoconstriction and also proliferation of vascular smooth muscle cells into the intima. Other renal causes of hypertension include stimulation of the renin-angiotensin system, prostaglandin inhibition, the hepatorenal syndrome, and pre-existing renal disease.

In the Addenbrooke's (Cambridge)/King's College Hospital (London) experience of 91 paediatric liver transplant patients between December 1983 and August 1989 the overall incidence of postoperative hypertension was 30%. The incidence was considerably higher in children with α_1 antitrypsin deficiency (71·5%) than in children with biliary atresia (22·5%) and the degree of hypertension was far more severe, causing hypertensive encephalopathy in four patients, the only patients in the series who developed this complication. The five children with α_1 antitrypsin deficiency described in this study had normal preoperative blood pressures with the exception of case 3 in whom a moderately raised blood pressure was observed once.

Postoperatively all the patients developed severe hypertension that was difficult to control (figs 1–5). In all except case 2 the onset was between the third and fifth postoperative day. Case 2 lost huge volumes of ascites from the fifth to the 22nd postoperative day and vasoactive substances as well as drugs were probably washed out. Certainly his cyclosporin doses had to be increased significantly and the measured protein content in the ascitic fluid was 50 g/l. All five patients developed acute graft rejection and received between one and three courses (total 13) of high dose steroid treatment. On nine occasions, steroid treatment, including the single dose of methylprednisolone given during the operation, was followed by an appreciable rise in blood pressure which reached its peak between the third and sixth days after the first dose and was associated with an increase in weight and ascites. Antihypertensive treatment often had to be increased during these exacerbations. Four hypertensive episodes were associated with a fall in creatinine clearance, which reached its lowest value either before or on the day of the maximum blood pressure. This suggested that renal arteriolar vasoconstriction may have preceded the onset of hypertension. Renal mechanisms seemed likely to be responsible, probably mediated either by stimulation of the renin-angiotensin system, by augmentation of thromboxane A_2, or by alteration of renal prostaglandin synthesis after the administration of glucocorticoids.[13–16] All patients received a large dose of methylprednisolone (10 mg/kg) during the operation, followed by 2 mg/kg/day for 14 days. Suzuki *et al* observed noticeable increases in blood pressure in rats treated with dexamethasone.[13] The maximum blood pressure was seen between the third and seventh day and decreased after administration of either an angiotensin antagonist or converting enzyme inhibitor. Nasjletti *et al* and Grunfeld *et al* found that glucocorticoids also have a strong depressor effect on basal release of renal prostaglandin, which may contribute to vascular hyper-reactivity in glucocorticoid induced hypertension.[14 16] Also interesting in the context of this study is the observation of Ramos *et al* that rats with chronic renal failure showed a higher increase in systolic blood pressure after administration of a single dose of methylprednisolone than normal rats.[15] Another aggravating factor may have been reduced clearance of renin and aldosterone due to transiently disturbed hepatic function,[17] but liver function remained satisfactory in these five patients during the periods of hypertension.

Thus many mechanisms may have a role in the development of hypertension after liver transplantation. We have not observed life threatening hypertension, however, in any patient without signs of renal disease. Patients with pre-existing renal disease are likely to be more sensitive to mechanisms which lead to renovascular constriction. Development of either preoperative or postoperative renal failure increases postoperative mortality.[18] In these patients two episodes of postoperative renal failure occurred that were associated with severe hypertensive crises but not related to steroid treatment.

This series of patients suggests that the association of renal disease with the hepatic disease of α_1 antitrypsin deficiency in childhood is more common and more important than has been recognised, especially when such children come to transplantation. The renal disease can easily be overlooked as haematuria and proteinuria may be transient and routine renal function tests are often normal, as seen in our patients. Mean C3 concentrations (51 g/l) were unusually low in comparison with mean prothrombin time (17 sec), both reflecting hepatic synthesis. This suggested possible renal pathology as well as poor hepatic synthetic function.

The pathogenesis of glomerulonephritis in patients with α_1 antitrypsin deficiency remains uncertain. Moroz *et al* found no renal lesions in 16 postmortem examinations on children dying from cirrhosis without α_1 antitrypsin deficiency.[8] Similarly we have not observed haematuria or proteinuria in children with liver disease not caused by α_1 antitrypsin deficiency. The association between glomerulonephritis and α_1 antitrypsin deficiency thus seems to be more than mere coincidence. Mesangiocapillary glomerulonephritis type I is an immune complex disease clinically characterised by hypocomplementaemia, proteinuria and/or haematuria. The deposition of α_1 antitrypsin has so far only been found in patients with α_1 antitrypsin deficiency and may be specific for this group of patients.[8] Follow up examination of renal function and symptoms in our patients showed absence of haematuria and proteinuria and normal plasma creatinine concentrations four months after liver transplantation.

In assessing children for liver transplantation knowledge of pre-existing renal disease has important clinical consequences. The onset of hypertension must be anticipated and treated effectively before end organ damage occurs. The antihypertensive agents of first choice in this group of patients may change if future studies confirm raised plasma renin and angiotensin concentrations.[19] Renal function needs to be monitored closely, particularly when nephrotoxic drugs are given. Cyclosporin should be started at low doses and concentrations kept in the lower therapeutic range. Plasma creatinine concentrations can be misleading in the assessment of glomerular function in malnourished patients.[10] Preoperative plasma creatinine measurements were normal in all five patients and postoperatively reached abnormally high concentrations in only two patients, even though glomerular filtration rates measured by creatinine clearance dropped to low concentrations in all five patients.

The prognosis for idiopathic glomerulonephritis type I is serious as end stage renal failure develops in 15–50% of patients within 10 years.[20] With IgA nephropathy approximately 10–30% of patients go into end stage renal failure over a period of 20 years. Because of the limited number of cases reported it is unclear if these glomerulonephritides associated with α_1 antitrypsin deficiency have a similar rate of progression. Prospective studies are needed to examine the incidence and prognosis of glomerular abnormalities in liver disease caused by α_1 antitrypsin deficiency and other conditions. Measurement of factors known to have a role in renal hypertension, particularly renin and prostaglandins, may lead to more rational measures for its control. The long term prognosis in α_1 antitrypsin deficient children may be improved by urgent liver grafting once signs of renal involvement have occurred.

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Corticosteroids in primary tuberculosis with bronchial obstruction

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Abstract

The usefulness of prednisolone in combination with the modern potent antituberculous drugs has been studied in 29 children with primary lung tuberculosis and hilar adenopathy causing bronchial obstruction. These children were divided at random in two groups of 15 and 14 patients. Both groups were treated similarly except that one group received prednisolone. Both groups were very similar before the onset of treatment for most variables. Tuberculous infection healed in both groups but the group on steroids improved earlier and had significantly fewer complications, both on radiography and bronchoscopy. Only two of the patients on steroids still had progressive lesions: a very young baby probably because he developed two severe viral infections consecutively, and another infant of 7 months whose treatment was unreliable, as the parents were not very compliant. Some patients initially not treated with prednisolone improved only after it was given. Prednisolone treatment is not recommended when the reliability of the treatment cannot be guaranteed, as the hazard of harm would exceed the expected benefit.

Primary tuberculosis still occurs in our country, especially in people living in very poor conditions and in recent immigrant populations.[1] This has also been shown recently by epidemiologists in the USA.[1] In our department we have discovered about 100 new cases each year.

Children who are symptomatic for tuberculosis suffer mostly, among other complications, from hypertrophy of the hilar lymph nodes. These can compress bronchi and even disrupt and discharge their caseous content in the bronchial tree (fistulisation).[2–6]

There is little information about the usefulness of corticosteroids in the treatment of bronchial obstruction in primary tuberculosis and that available in recent papers[7] is often from old publications. In the 1960s there were claims for its efficacy, when given at the early onset of bronchial obstruction and before fistulisation, to prevent complications such as fistulisation and bronchiectasis.[2 3 8] Other authors such as Nemir *et al* did not confirm this beneficial effect in a preliminary study.[9] This study suffered from an uneven distribution of patients, and in a later study on a larger series of children the authors demonstrated a significant and noticeable improvement in tuberculous patients treated with steroids compared with those not treated with steroids.[10]

Steroids are neither harmless nor easy to control when needed for a prolonged period of time. Hypertension and water retention as well as potassium depletion are potential risks. Furthermore it is well known that premature and abrupt interruption of steroids is often followed by a severe 'rebound' reaction.[3 11] This can be even more severe than the initial lesion.[3]

We decided to undertake a new open trial to examine the use of steroids in bronchial obstruction (i) because more efficient antituberculous drugs are now available and it was not known whether steroids had a beneficial effect when used with these newer drugs and (ii) because of the controversy concerning the risks surrounding steroid use. The study was restricted to patients with primary tuberculosis and bronchial obstruction without fistulisation as we wanted to see whether fistulisation could be avoided by steroid treatment.

Patients and methods

A total of 29 patients (26 from immigrant families) were treated for symptomatic tuberculosis with severe bronchial obstruction suspected by radiology and demonstrated by bronchoscopy. Their ages ranged from 4 months to 15 years (median 7·8). There were 10 girls and 19 boys. This sex ratio was comparable with recent epidemiological figures.[1]

The diagnosis was established in all patients through a recent tuberculin conversion, using 2 IU of Rt 23 tuberculin, from the Statens Serum Institut of Copenhagen, injected intradermally. This test was positive in all subjects—that is, an induration of at least 10 mm after 48 or 72 hours. In 14 patients tuberculin tests were performed because of clinical signs such as an unexpected course of pulmonary consolidation, long standing unexplained fever or cough, and in nine patients because of a recent positive family history of tuberculosis. Only in six patients was severe primary tuberculosis diagnosed through a routine and systematical tracing at school.

Chest radiographs were available for all patients before treatment and in 23 at one, two, three, six, nine, and 12 months after starting the treatment. The radiological findings were arbitrarily codified to measure objectively and uniformly the extent of the pulmonary involvement. The size of the adenopathy was scored from 1 to 3, segmental consolidation or hyperinflation scored 1, lobar consolidation or hyperinflation scored 3, and pulmonary consolidation or hyperinflation scored 6. These scores were added up to obtain the total radiological

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score. All radiographs were read 'blind' separately by the two paediatric radiologists (MS and VT).

Bronchoscopy was also performed blind by the two paediatric respiratory physicians (ID and AM) on all patients with abnormal radiological findings. Rigid bronchoscopy (bronchoscopes with Johns Hopkins telescopes, Storz Germany) was performed under general anaesthesia for patients younger than 5, and flexible fiberoptic bronchoscopy (BF 3 C 10 and BF P 10, Olympus Japan) was performed in the older patients under local anaesthesia. Bronchoscopy findings were scored depending on the localisation and the extent of the compression as shown in table 1. Patients who already had bronchial fistulisation were not included in this study as the aim was to verify whether fistulisation could be prevented. Patients with meningitis, or miliary tuberculosis, were also excluded. Patients without clinical and radiological abnormalities and negative bacteriology for *Mycobacterium tuberculosis* did not need bronchoscopy and were not eligible for the study. Only those 29 patients with a compression of at least 50% of a bronchus and with a bronchoscopy score (see table 1) equal or higher than 2 have been selected for this trial. The endoscopy was repeated at least after one or two months of treatment in all of them and, when the course was unfavourable, even more often.

Antituberculous treatment consisted of a combination of isoniazid (10 mg/kg body weight/day to a maximum 300 mg/day) and rifampicin (15 mg/kg body weight to a maximum 600 mg/day) for one year and ethambutol for two months (20 mg/kg body weight/day) providing there was no visual disturbance. Treatment was systematically adjusted whenever there was a positive culture and when sensitivity testing in vitro showed that the previous choice was not appropriate.

Table 1 Bronchoscopy score

	Score
(A) Localisation:	
Trachea	4
Main bronchus	3
Lobar bronchus	2
Segmental bronchus	1
(B) Importance of the obstruction:	
Total or >75%	4
50–75%	2
<50%	1
No obstruction	0

The bronchoscopy score=$\Sigma(A\times B)$.

Patients were divided into group 1 (steroid treatment) or group 2 (no steroid treatment) by previously randomised and numbered envelopes.

STEROID TREATMENT

Prednisolone was started at a daily dose of 2 mg/kg of body weight for 15 days and was progressively decreased to be stopped between 2·5 and 3 months. We had previously observed that within a few days of too early or abrupt an interruption of steroids patients often showed a severe rebound reaction. Sometimes there were even more extensive lesions than before the onset of prednisolone and the hazard of fistulisation had also increased.

Paediatric endocrinologists recommended that these children receiving such high doses of corticosteroids for more than one month should have a sodium restricted diet and that they should also receive potassium gluconate supplements and gastric protection by aluminium phosphate.

FOLLOW UP

A few children were admitted to hospital before the start of the trial for either bronchoscopy under general anaesthesia or because of their poor general condition. All drugs were taken orally. To guarantee optimal therapeutic compliance, which was essential in the steroid group where side effects due to incorrect diet could be dangerous, and to ensure that patients were seen as scheduled, a special home care unit was set up by MT.[12]

GROUP 1 (STEROIDS)

This group comprised 15 children (11 boys, four girls) aged 4 months to 12 years (median 6·3 years). Two were lost to follow up after six months (table 2).

GROUP 2 (NO STEROIDS)

This group comprised 14 children (eight boys, six girls) aged 18 months to 15 years (median

Table 2 Characteristics of the patients treated with steroids (group 1)

Case No	*Age (years)*	*Mycobacterium tuberculosis*	*Extra lesions at onset seen on radiology*	*Score on radiology*	*Score on bronchoscopy*	*Comments*
1	10·0	+		3	17	
2	4·0	+	Lobar consolidation	3	16	Lost to follow up after 3 months
3	1·8	–	Segmental hypoventilation	4	26	
4	1·5	+		3	2	
5	1·5	+	Lobar consolidation	5	10	
6	7·0	+	Segmental consolidation	3	4	
7	0·3	+	Multiple consolidation	10	16	Measles, respiratory syncytial virus infection, fistulisation
8	12·0	+	Lobar consolidation	6	24	
9	8·0	–	Pulmonary hypoventilation	9	26	Lost to follow up after 2 months
10	0·8	–	Lobar consolidation	6	15	
11	0·3	+	Segmental hypoventilation	4	15	
12	0·6	–		3	12	Bad compliance, fistulisation
13	4·0	–	Segmental consolidation	3	16	
14	11·0	–	Lobar consolidation	6	18	
15	2·0	+	Segmental consolidation	4	14	

Table 3 Characteristics of the patients treated without steroids (group 2)

Case No	*Age (years)*	*Mycobacterium tuberculosis*	*Extra lesions at onset seen on radiology*	*Score on radiology*	*Score on bronchoscopy*	*Comments*
1	5·0	+	Segmental consolidation	4	12	Steroids given after 1 month
2	15·0	+	Segmental consolidation	4	5	
3	7·0	+		3	21	Fistulisation
4	8·0	+	Lobar consolidation	6	8	Fistulisation
5	3·0	+	Multiple consolidation	5	16	Steroids given after 1 month
6	3·0	+	Lobar consolidation	6	9	
7	9·0	+		2	10	
8	3·0	−	Bilateral adenopathy	3	14	
9	0·5	+	Segmental consolidation	4	9	Fistulisation, lost to follow up after 3 months
10	3·0	−		2	13	Lost to follow up after 6 months
11	5·0	+	Segmental consolidation	3	19	Steroids given after 1 month, lost to follow up after 6 months
12	2·0	−		3	20	Steroids given after 1 month
13	1·5	−		3	3	
14	12·0	−	Lobar consolidation + pleural effusion	6	6	Lost to follow up after 8 months

8·3 years). Ten had a regular follow up in our home care clinic; four were followed up elsewhere or left the country and their data were incomplete and not used for statistical analysis (table 3).

STATISTICAL ANALYSIS

Statistics were performed by MPD. All tests were carried out two tailed at the 5% level of significance. The Mann-Whitney test was used to evaluate the similarity between the two treatment groups at the start of the study and to compare the change of the variables during treatment in both groups. The course of the variables within each of the groups was investigated by the Wilcoxon test. In order to compare the number of patients showing an improvement on radiology in both groups, Fisher's exact test was used.

ETHICAL COMMITTEE

The ethical committee did not consent for double blind study because:

(1) Before the trial corticosteroids were used routinely in all patients with bronchial obstruction in primary tuberculosis and therefore patients without steroids should be known and given the possibility to interrupt the trial in case of their condition deteriorating.

(2) Patients taking corticosteroids should have sodium restricted, potassium enriched diets and patients without steroids should not.

Results

Tables 2 and 3 illustrate the characteristics and course of the children in the two groups.

RADIOLOGY (TABLE 4)

Because of incomplete radiological follow up over the planned treatment period, and despite complete bronchoscopic follow up during the first months of the study, information on six of the original 29 patients was not sufficient for statistical analysis (two in group 1, four in group 2, not significant by Fisher's exact test). Radiological follow up over 12 months was available for the remaining 23 patients. After one month of treatment the number of improved radiographs was significantly higher in group 1 (7/13) than in group 2 (0/10) (p=0·0075 by Fisher's exact test). Normalisation after three months was significantly higher in group 1 (7/13) than in group 2 (0/9) (p=0·04). One child in group 2 who became normal was given steroids one month after the onset of treatment and he was not included in the statistical evaluation in any group.

Table 4 Course of radiological score

	Group 1 (steroids)	*Group 2 (no steroids)*
No of subjects	13	10
Improvement seen ≤1 month	7	0
Normalisation seen:		
≤3 Months	6	(1)*
Between 3 and 6 months	3	(2)*
Between 6 and 12 months	4	6
Deterioration during treatment	2	5
Sequels	0	1

*After the addition of steroids for the appearance of lobar consolidation and increased score on bronchoscopy.

BRONCHOSCOPY (TABLE 5)

Information was available for all 29 patients after one month of treatment. Bronchoscopy scores decreased significantly in both groups (respectively p=0·0007 and p=0·003 for group 1 and for group 2 on the Wilcoxon test). A comparison of the grade of the change by means of the Mann-Whitney test, however, indicated a more important decline in group 1 than in group 2 (p=0·003).

Some data are worth mentioning, though not clearly represented on the tables and not used for statistical evaluations, are that three children from group 2 (cases 3, 4, 9) developed fistulas and granulomas within one month and needed several bronchoscopies and extraction with forceps before the airways became completely clear again. Four children (cases 1, 5, 11, 12) who were randomised in group 2, worsened on both evidence from the radiographs and bronchoscopy despite one month of correct antituberculous treatment and eventually corticosteroids were added to their treatment. They then improved but to avoid any bias they were not included for statistical evaluation in group 1. In group 1 one patient (case 12), known for his poor therapeutic compliance, developed a

Table 5 Course of bronchoscopy score

	Group 1 (steroids)		*Group 2 (no steroids)*	
	Before treatment	*After 1 month treatment*	*Before treatment*	*After 1 month treatment*
Mean (SD)	14·7 (7·3)	2·7 (3·9)	11·8 (5·7)	5·9 (6·5)
Mean (SD) difference	12·1 (6·9)		5·9 (5)	
Wilcoxon	p=0·0007		p=0·003	

bronchial fistula after three months. Another patient from the same group (case 7), who developed successively measles and respiratory syncytial virus infections at the fourth month after the start of the treatment, then showed bronchial fistulisation, despite perfect therapeutic compliance. In fact these two children showed fistulisation after the end of the steroid treatment and not during it.

The number of children who needed more than two bronchoscopies was appreciably higher in the group not taking steroids than in the steroid group (six patients compared with one).

Discussion

In our department most of the children with primary tuberculosis come from a high risk group. They are mostly immigrant families, originating from underdeveloped countries, though the infection often takes place in our country because of bad housing and working conditions. This accounts for the very high rate of 18 positive cultures for *M tuberculosis* on these 29 patients and is also representative of the severity of the clinical symptoms and radiological abnormalities at the onset of the diagnosis.

The relatively small number of drop outs, despite the fact that many families could not express themselves in one of the local languages, can be attributed to the home care structure stimulating trust and enabling a close and correct drug monitoring.[12]

There is a relatively clear agreement on how to use the different specific antituberculous drugs in monotherapy or in combination, depending on the clinical picture.[4 5 7 13] The aim of our study was not to re-evaluate this and anyway all our patients were cured of their infection, whether steroids were added or not. Our goal was limited to the examination of the effect of prednisolone on bronchial compression by lymph nodes before the disruption occurred. Nemir *et al* also showed an effect on the course after fistulisation,[10] but we preferred not to include the latter in order to have a homogeneous series needing fewer patients.

The beneficial effect of corticosteroids in combination with antituberculous drugs is well known in important pleural effusion.[3–5]

Adding corticosteroids in the first three months of antituberculous treatment has also been studied in adults with advanced cavitary pulmonary tuberculosis, and showed a favourable influence on radiological and clinical course and on pulmonary function.[11] Despite older and less active tuberculostatics these patients did not run a greater risk.

As stressed in the introduction, little information is available about the usefulness of corticosteroids in childhood primary tuberculosis, and we were not able to find any recent study. Nemir *et al* in 1963 were not capable of demonstrating any benefit on a small series of children.[9] These authors concluded that the steroid group suffered more severe lesions than the group not on steroids as was clearly shown in the significantly larger number of patients positive for *M tuberculosis* in the group on steroids: 'In general, the prednisone-treated group was more severely ill as judged by the greater frequency of cultures positive for tubercle bacilli, obtained chiefly before steroid therapy, and the presence of other diseases before adjunct therapy was initiated . . .'. In a second study in 1967 by the same group on a larger series of children 'a higher percentage of marked improvement occurred among the steroid treated group, namely 36% compared to 15% in the control group (p<0·05)'.[10] However the steroid group suffered several side effects such as hypertension, excessive weight gain, and 'moonface'; none of these side effects was seen in our study. In 1965 Gerbeaux *et al* also claimed that steroids were beneficial on a very large series of children.[2 3]

Our study showed a more even distribution of the patients in two comparable samples to that of the patients reported by Nemir *et al* in their preliminary study. There were no significant bacteriological, radiological, or bronchoscopic differences between our two groups before the onset of any treatment (tables 2 and 3). The only difference was that the steroid group was slightly younger and therefore may be at a higher possible risk for complications. Otherwise the severity of the disease was similar in both groups and the beneficial effect of the steroid treatment as reflected by the different course or outcome is certainly neither coincidental, nor due to any bias.

This modest study, performed on a small number of patients, still clearly demonstrates the benefit of adding prednisolone whenever bronchial compression is demonstrated, and before airways are damaged by caseous fistulas, even though all patients were given a combination of very active antituberculous drugs including rifampicin, not used in the previous studies. Though in both groups the bronchial lesions improved significantly under treatment, it was faster and more noticeable in the steroid group. Moreover, the risk of complications known to occur on steroid treatment appeared only during uncontrollable or unexpected events, such as severe viral superinfection or poor therapeutic compliance. On the contrary, in the group not taking steroids, fistulisation occurred more often and on a few occasions previously mild compressions worsened and these improved only after the addition of prednisolone. Cushing's syndrome has never been seen in our patients, thanks to a thorough salt restricted diet and other precautions.

We conclude that whenever severe bronchial compression has been demonstrated, steroids remain beneficial and should be added to the specific antituberculous treatment notwithstanding the available powerful antituberculous drugs and despite the fact that this will increase the load of the treatment. The benefit was sufficiently noticeable and significant even in this small series to consider it unethical to continue the trial. All eligible patients should benefit from steroid treatment under optimal conditions.

The patient's or family's compliance should be carefully evaluated before starting steroids, as the risk of damage as a consequence of poor administration or an incorrect diet would be greater than the expected benefit. Patients with bronchial compression not receiving steroids should be carefully and closely observed, as they will perhaps need more therapeutic bronchoscopies.

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Virological investigations of acute encephalopathy in India

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Abstract

A total of 740 consecutive children aged between 6 months and 12 years who presented with acute encephalopathic illnesses during a three year period were assessed both clinically and by laboratory investigations. Cerebrospinal fluid was examined for the presence of cells or other abnormal substances, and any organisms were cultured. Blood examination included white cell count and estimations of haemoglobin, urea, glucose, and electrolyte concentrations and serum alanine aminotransferase and aspartate aminotransferase. A firm diagnosis was established in 278 patients (38%). Pyogenic meningitis (n=134), measles encephalopathy (n=38), and electrolyte imbalance (n=23) were important causes in this group, cerebral malaria (n=4) was uncommon and there were no cases of Reye's syndrome. The diagnoses of the remaining 462 were combined under the heading 'acute unexplained encephalopathy'. Altogether 394 of the 462 patients underwent virological investigations for arboviruses and 92 (23%) had one or more indicators of Japanese encephalitis. No other arboviruses could be isolated. Throat swabs from 187 patients with acute unexplained encephalopathy were studied on monkey kidney tissue cell lines of which 14 were positive (8%). These were identified as adenovirus, parainfluenza, influenza, poliomyelitis, Coxsackie, and echovirus; in two cases the virus was untypable.

Japanese encephalitis is an important cause of acute childhood encephalopathy in this region. Clinical features of the illness may be mimicked by several disorders which require specific treatment. Thirty four of the 92 died (37%).

Acute encephalopathy is an important cause of admission to hospital and death as well as being a public health problem in India.[1] Several unrelated disorders (such as bacterial and viral infections of the central nervous system, Reye's syndrome, cerebral malaria, and electrolyte imbalance) may present as acute encephalopathy in children. There were, however, no comprehensive, systematic studies of the aetiology of childhood encephalopathies in India, and in 1979 the Indian Council of Medical Research put forward recommendations for the conduct of research on these encephalopathies.[1]

The present study was designed to investigate the aetiology of acute childhood encephalopathy by examining all those who presented to a large city hospital in northern India where it is an important problem.

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Patients and methods

Consecutive children between 6 months and 12 years of age admitted to the paediatric wards of the King George's Medical College, Lucknow, were included in the study if the main complaint was an acute constant depression of consciousness lasting for more than 12 hours, and the total duration of illness at the time of admission was one week or less.

The King George's Medical College is a large teaching hospital that caters mainly for the lower socioeconomic group and seriously ill patients from Lucknow city and district as well as the surrounding districts. About two thirds of the patients admitted come from rural areas.

Histories were taken on admission and the information was entered on a proforma, together with the results of the physical examination. A careful record of the patients' progress in hospital was maintained. An attempt was made to determine the cause of the illness from the results of the following investigations: the cerebrospinal fluid was examined for the presence of cells, protein, glucose, and organisms; full blood counts were done including examination of a peripheral smear for the presence of *Plasmodium falciparum* and serum concentrations of urea, glucose, and electrolytes were estimated together with the activities of alanine aminotransferase and aspartate aminotransferase. Enzyme activities were estimated when there was no sign of pleocytosis in the cerebrospinal fluid, and when no other cause could be found for the encephalopathy. Blood was cultured when indicated.

Other investigations such as computed tomography were done when indicated and possible. Patients whose diagnosis was not evident after these investigations had been carried out were termed 'acute unexplained encephalopathy' and virological investigation was carried out.

The following samples were collected for virological investigations: cerebrospinal fluid; brain tissue whenever possible by necropsy brain biopsy; serum samples during the acute and convalescent phases, and throat swabs in minimum essential medium.

All samples were kept at 2–8°C and transported within 24 hours in ice to the virology laboratory of the King George's Medical College, which is one of the national reference laboratories for arboviruses. Viral isolation was attempted from cerebrospinal fluid and brain tissue by intracerebral inoculation into 1–2 day old mice. Identification of the virus was done by the quick complement fixation test using the brain suspension of sick mice as a crude antigen against hyperimmune sera of West Nile virus,[2] Dengue virus serotypes 1, 2, 3, and 4, Japanese encephalitis, and Chikangunya viruses. These samples were obtained from the National Institute of Virology, Pune.

The haemagglutination inhibition test for Japanese encephalitis was done on paired serum samples.[3 4] A four fold or higher rise in the antibody titre of Japanese encephalitis virus was considered to be highly suggestive of the infection. Serum with positive haemagglutination inhibition (that is, a fourfold or higher rise in haemagglutination inhibition antibodies in paired samples) were retested after treatment with 2-mercaptoethanol to look for specific anti-Japanese encephalitis virus IgM antibodies. Patients with both a positive haemagglutination inhibition test and detectable anti-Japanese encephalitis virus IgM were considered to have positive serology. Details of virological methods have been described previously.[5]

Throat swabs were inoculated into primary monolayer cultures of renal epithelial cells from Rhesus monkeys and examined for their cytopathogenic effect according to standard virological methods. Identification of viruses was done by the haemadsorption inhibition and neutralisation tests in tissue culture using standard hyperimmune serum samples obtained from Wellcome Reagents, London, and the Haffkine Institute, Bombay.[6 7]

Results

During the three year period August 1985 to August 1988 a total of 740 children was enrolled in the study. Another 42 children satisfied the study criteria but could not be investigated because they died too soon after reaching the hospital or left against medical advice. None of these children had clinical features that suggested the cause of their encephalopathy (for example, poisoning, head injury, or hypertension). In 278 of the 740 patients investigated (38%) a firm diagnosis was reached after the clinicopathological investigations outlined above, the various diagnoses are shown in table 1. The diagnosis of the remaining 462 patients were grouped under the heading 'acute unexplained encephalopathy' and 394 of these underwent virological investigations for arboviruses. Viral isolation was attempted from cerebrospinal fluid in 315 patients, from brain tissue in 25 patients, and from paired serum samples (which could be only obtained from 174 patients). Throat swabs were obtained from 187 patients. Results of the virological investigations are shown in table 2.

Table 1 Diagnoses in 370 patients

Confirmed diagnoses	*No of patients*
Bacterial meningitis	134
Tuberculous meningitis	21
Measles encephalopathy	38
Electrolyte imbalance	23
Prolonged coma after seizures	16
Hepatic encephalopathy	8
Shigellosis	8
Poisoning	7
Mumps encephalopathy	5
Miscellaneous	5
Cerebral malaria	4
Enteric encephalopathy	4
Hypertensive encephalopathy	3
Head injury	2
Reye's syndrome*	0
Total confirmed diagnoses	278
Japanese encephalitis	92
Total	370

*Electrolyte concentrations were estimated in 412 patients and serum enzyme activities in 414.

Table 2 Results of virological investigations

No of patients with possible viral encephalitis	462
No of patients examined for arboviruses	394
No of patients with indicators of Japanese encephalitis infection:	92
Virus isolated from brain alone	5
Virus isolated from cerebrospinal fluid alone	22
Positive serology alone	59
Positive serology and isolation of virus	6
No of patients examined for other viruses (by throat swab inoculation into monkey kidney tissue cells)	187
No of patients positive for other viruses:	14
Adenovirus	5
Parainfluenza	3
Influenza	1
Polio	1
Coxsackie	1
Echo	1
Untypable	2

Discussion

One problem of the study of encephalopathies is the terminology used to describe the illness. A number of such clearly characterised diseases as pyogenic meningitis, tuberculous meningitis, and Reye's syndrome may produce similar clinical pictures of acute depression of consciousness with or without other neurological findings. For this reason we have used the general term 'acute encephalopathy' as it is less restrictive as a preliminary diagnosis of a syndrome that has many possible causes. When known causes have been excluded, the term 'acute unexplained encephalopathy' has been used.

There are few studies of this kind from the Indian subcontinent. Mehrotra *et al* described virological, bacteriological, haematological, and epidemiological investigations in 61 patients with 'pyrexia and disturbance of conscious state often leading to coma'.[8] They found local or systemic bacterial infection in 30 patients and isolated viruses from seven. They concluded that the syndrome had a varied aetiology, an important cause being acute toxic encephalopathy secondary to bacterial infection. Benakappa *et al* studied 64 children with a 'clinical picture of encephalitis' by serum biochemical investigations including estimation of enzyme activities and virological investigations.[9] John *et al* studied 255 patients with acute encephalopathic illnesses and attempted to isolate viruses from throat and rectal swabs, cerebrospinal fluid, blood, urine, and tissues.[10] The present study is the first systematic long term, comprehensive study of the aetiology of acute childhood encephalopathy in India and was designed to conform to the guidelines of the Indian Council of Medical Research task force recommendations for research on encephalopathies in children.[1]

In this study we enrolled consecutive cases with acute encephalopathic illness, and in this sense our cases were unselected. The 42 patients who could not be studied were mostly patients with unexplained encephalopathies, as none had an obvious cause for the illness. Infants below the age of 6 months were excluded from study because young babies often present with alteration of consciousness with non-neurological disorders. Only patients with continuing alteration of consciousness for more than 12 hours were entered into the study. This excluded most cases of simple convulsions.

The diagnosis of bacterial meningitis was firmly established in 134 patients, and was made because of cerebrospinal fluid turbidity and cell count, glucose concentration, or the presence of organisms. Clinically bacterial meninigitis may be indistinguishable from encephalopathies such as cerebral malaria or viral encephalitis. Even examination of the cerebrospinal fluid may not differentiate it from these conditions, especially if antibiotics have been given. Thus a few of our patients who were later proved to have viral encephalitis had received treatment for bacterial meningitis.

Tuberculous meningitis usually has a gradual onset and patients are generally not admitted to hospital within a week of the onset of the illness. Occassionally patients have short histories and such cases may be difficult to differentiate from viral encephalitis unless more detailed studies are undertaken. Our cases of tuberculous meningitis were diagnosed from other indicators of tuberculous infection with or without computed tomographic evidence of basal exudates.

After excluding meningitis, a small but important group were those patients with measles associated encephalopathy, which may be caused either by measles virus invasion of the central nervous system or by an allergic demyelinating reaction.[11] Of the 38 patients with this illness 28 presented within 10 days of the onset of the measles rash.

Cerebral malaria was found in only four patients in the present series, and was diagnosed by the presence of *P falciparum* in the peripheral blood smear. Lucknow is not an endemic area for malaria, having an annual parasite index of less than 2 (State Malaria Department, Uttar Pradesh), which explains the low occurrence of cerebral malaria in this region.

Twenty three children had electrolyte imbalances: hyponatraemia (serum sodium less than 125 mmol/l, n=12) and hypernatraemia (serum sodium greater than 150 mmol/l, n=11). These were usually associated with diarrhoea or vomiting, or both, and were probably the cause of the encephalopathy. Another two patients had hyponatraemia but were later found to have Japanese encephalitis as well.

An important finding was that not a single case of Reye's syndrome was diagnosed during the three year study period, although 414 patients were 'screened'. Serum enzyme activities serve as a useful screening test for this disorder. Although increases in serum transaminase activities do not by themselves establish the diagnosis, they are usually raised in almost all cases. Corey *et al* found increased serum aspartate transaminase activities in all their 397 patients with Reye's syndrome whereas increased serum ammonia concentration was not an invariable finding.[12] It is possible that several tests may be more useful than one single test, and a few cases may have been missed, but it does seem that this illness is uncommon in Lucknow. Reye's syndrome was diagnosed in 15 of 19 children with a 'clinical picture of encephalitis' studied by estimation of serum enzyme activities in Bangalore.[9] In Delhi, 12 of 80 patients (15%) with 'encephalitis or encephalopathy syndrome' were diagnosed as having Reye's syndrome and this was confirmed by histopathological examination[13]; cases have also been reported in Nagpur,[14] Bombay,[15] and Chandigarh.[16] Our findings suggest that the aetiology of this illness may vary in different parts of the country.

Heat stroke was considered to be the cause of 'acute encephalopathy syndrome' in another hinterland (Nagpur) in the hot summer months. Sriramachari and Patoria carried out neuropathological examinations of brains removed at necropsy from 15 such children and found changes that were consistent with 'effects of pyrexial damage rather than any inflammatory process'.[17] Although histopathological studies were not done in the present investigation, our patients did not have temperatures high enough to suggest this diagnosis. In addition, most of the cases presented in the late monsoon season rather than the summer.

Japanese encephalitis was first recognised in India in the mid 1950s. The first serious epidemic occurred in West Bengal in 1973, and since then several epidemics have occurred in the eastern and southern parts of the country.[18] In 1978 there was a large epidemic in Uttar Pradesh, indicating inland spread of the disease.[5] A report of the first 86 patients in the present study showed that Japanese encephalitis is an important cause of childhood encephalopathy in the Lucknow region, with cases occurring throughout the year.[19] Specimens from our patients with unexplained encephalopathy were therefore investigated for evidence of Japanese encephalitis and related arboviruses. A total of 92 cases of Japanese encephalitis out of 394 studied were identified (23%); no other arboviruses could be isolated. Japanese encephalitis is thus a serious cause of acute childhood encephalopathy in this region. Cases were seen all the year round with a peak incidence in the months after the monsoon—that is, October/November when the mosquito population is at the peak. Nearly half the cases came from the towns, and 34 of the 92 died (37%).

Other viruses such as adenovirus, paramyxovirus, and enteroviruses were isolated from throat swabs of 14 of 187 patients examined (8%), and may have been responsible for their illnesses. Benakappa *et al* found five isolates of Coxsackie virus in rectal swabs and one in cerebrospinal fluid in 64 of the cases of acute encephalopathy examined.[9] John *et al* isolated enteroviruses from the cerebrospinal fluid of eight children, from brain tissue in three children, and from other sites (for example, throat swabs and rectal swabs) in nine of 255 children with encephalopathy.[10] Hardas *et al* found enteroviruses in 14 of 90 cases of encephalitis.[20] Enteroviruses do therefore occasionally seem to be responsible for viral encephalitis in this country.

The cause of encephalopathy remained undetermined in about 40% of the children despite the investigations outlined. Japanese encephalitis could not be ruled out in some of these because the rate of viral isolation from cerebrospinal fluid is not high even under the best conditions. Paired serum samples could not be obtained from many patients who either died in the acute stage of the illness or recovered rapidly and were discharged from hospital before a convalescent sample was taken. Investigation for viral infections other than Japanese encephalitis was incomplete in this study, because serological tests for antibodies to other viruses were not carried out. This would have increased our ascertainment of infection by other viruses in the same way as it did for Japanese encephalitis. Investigations were therefore restricted to arbovirus, enterovirus, and viruses affecting the respiratory tract. Other disorders such as arterial or venous occlusions, intracranial haemorrhage, metabolic disorders such as systemic carnitine deficiency, defects in amino acid synthesis or organic acidaemias, and lead intoxication may also present as encephalopathy, and may have caused the illness in some of our patients.

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Perianal appearances associated with constipation

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Abstract

The perianal appearances were studied prospectively of 136 constipated children (mean age 3·9 years, 67 boys, 69 girls). Anal dilatation, fissures, tags, warts, perianal oedema, redness, blueness, and veins were recorded. It was noted whether dilatation occurred immediately or at 30 and 60 seconds with the buttocks minimally separated, and on subsequent firm lateral traction of the buttocks. The degree of faecal loading was assessed in all children. Anal dilatation was found in 24 (18%) and first appeared on lateral traction in eight (6%). In three quarters of the children with dilatation faecal loading or perianal signs were present. Fissures were found in 35 (26%) children and tags in seven (5%). Perianal redness was more likely to be associated with fissures, and blueness with dilatation.

We conclude that there are no pathognomonic perianal signs in childhood constipation and that the technique of anal examination should be standardised.

Although constipation is a common disorder in childhood, we know of no detailed description of the perianal appearances. Such information is urgently required, as the physical signs seen in constipated children may be similar to those found in the victims of sexual abuse. Hobbs and Wynne reported the presence of reflex anal dilatation or a dilated anus in 22 of 35 sexually abused children (63%), fissures in a similar number, and venous swelling with blue discoloration of the perianal skin.[1] In a further series these authors reported 337 confirmed or probable victims of childhood sexual abuse of whom 143 (42%) had anal signs.[2] Of those with anal signs 42% had anal dilatation, 53% had fissures or tears, 53% had perianal reddening, 38% had anal laxity, 24% had venous congestion, 8% had scars or tags, and 4% had warts.

In a retrospective analysis of 129 severely constipated children (all tertiary referrals), Clayden reported anal dilatation in 15% with a clear association between faecal loading and dilatation.[3] A fissure was recorded in one patient, although smaller fissures may have been present in others as only the most prominent anal findings were recorded (G S Clayden, personal communication). In a series of 343 severely constipated patients followed up over many years anal fissures were the most striking perianal characteristic in 6% and anal tags in 3% (G S Clayden, unpublished observations).

Anal dilatation has also been reported in children who were not being investigated for childhood sexual abuse or constipation. McCann *et al* investigated 267 normal prepubertal children and found anal dilatation in 49% (mean observation time four minutes, range up to eight minutes); only 15% of these children showed signs of dilatation within 30 seconds, and 27% within two minutes.[4] None of the subjects had anal fissures. Stanton and Sunderland investigated 200 children attending community, general paediatric, and renal clinics and found that 14% had reflex anal dilatation.[5] These authors found four children with fissures, although three of these were also constipated.

As examination techniques are not uniform and descriptive terms not always precise, it is possible that different authors have reported different phenomena.[6] We have therefore prospectively examined children referred because of constipation to establish the incidence and characteristics of perianal signs.

Patients and methods

One hundred and thirty six children were examined over a period of one year. All had constipation and 133 were referrals from general practitioners. The mean age was 3·9 years (range 6 weeks to 13 years), and 53 (39%) were under 2 years of age. There were 67 boys and 69 girls and the duration of symptoms ranged from six weeks to nine years. All children were examined in a hospital outpatient clinic with one or both parents present and the examination was a routine part of the initial assessment. The examination was standardised and carried out by the same person (UA) in all cases. Children under the age of 2 years were examined supine, and older children in the left lateral position. The examination lasted a little over a minute. For the first 60 seconds the child's anus was observed with the buttocks minimally separated and it was noted when dilatation was first seen and for how long it lasted. After 60 seconds firm lateral traction was applied to the buttocks and any effect on the anus noted. No child was examined in the knee-elbow position.

We also recorded whether dilatation was full (relaxation of both anal sphincters) or partial (relaxation of the external sphincter only). When dilatation is full the rectum can be seen through the anal canal; when it is only partial the anal canal alone can be seen, as if looking into a hollow cone. The latter finding is distinct from the mandatory relaxation of the external sphincter, which occurs after voluntary constriction of that sphincter. It can also be distinguished from the lax and often open anus seen in

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neurological conditions such as meningomyelocele.

Apart from dilatation we looked for anal fissures (defined as a breach in the squamous epithelium of the lower third of the anal canal),[7] anal skin tags, anal warts, perianal oedema, perianal veins, and perianal discoloration. No instruments were used during the inspection. The number, age, and location of fissures, the number and location of skin tags, the prominence (visible, prominent, or varicose) of veins, and degree of perianal discoloration (redness—faint, definite, or angry; blueness—faint, definite, or deep) were recorded.

The degree of faecal loading was assessed by abdominal palpation and rectal examination and graded by Clayden's method: no stool palpable in the abdomen=grade 0; small suprapubic mass=grade 1; stool palpable half way up to the umbilicus=grade 2; stool palpable up to the umbilicus=grade 3; stool palpable a third of the way from the umbilicus to the xiphoid process=grade 4; stool palpable two thirds of the way from the umbilicus to the xiphoid process=grade 5, and stool palpable at the rib cage=grade 6. Rectal loading was found only in those patients with faecal abdominal masses.

The χ^2 test was used to assess the significance of differences between groups.

Results

DILATATION

Twenty four children (18%) had some degree of anal dilatation (full or partial) during the observation period, and 17 of these were girls. Their mean age was 2·8 years, range 2 months to 11·5 years. The timing of dilatation is shown in table 1, and the correlation between dilatation and faecal loading in table 2. Spontaneous dilatation occurred either immediately or at about 30 seconds. When dilatation occurred it usually lasted at least 15 seconds (often a minute or more), regardless of whether it was full or partial. There was no association between length of dilatation and faecal loading. The anuses of eight children only became dilated when firm lateral traction was applied to the buttocks and five of these had detectable faecal loading (two had full dilatation). Anal fissures were seen in five of the eight, and a small rectal prolapse and an anal tag were seen in one patient each. Three children had no perianal signs and two of these had no faecal loading. Seven of the eight children had no dilatation on follow up examination two weeks later.

Fourteen children had dilated anuses without faecal loading; nine of these had partial dilatation and five had full dilatation (table 2). Of the nine with partial dilatation, five had fissures but the other four had no abnormal perianal signs. Of the five with full dilatation, one had a rectal prolapse and two had anal fissures, but in the other two children no obvious perianal signs were found. In none of the five children with full dilatation was dilatation seen on follow up examination two weeks later. Seven of the nine children with partial dilatation were also reexamined and three showed full dilatation, but had faecal loading at that time. Ten children had some degree of faecal loading with either partial (n=4) or full (n=6) dilatation. Anal fissures were found in only three (one full and two partial dilatations), a tag and a fissure in one (partial dilatation), and six children had no perianal features. There were 36 children who had faecal loading without dilatation.

ANAL FISSURES

Anal fissures were found in 35 children (26%); their mean age was 2·8 years, range 2 months

Table 1 Onset of full or partial dilatation during a 60 second observation period followed by lateral traction of the buttocks in 24 patients

	Full dilatation	*Partial dilatation*	*Total No of dilatations*
Dilatation:			
Seen immediately	3	2	5
Seen at 30 seconds	4	7*	11*
Seen at 60 seconds	0	0	0
Seen on lateral traction	4*	5	9*
Total No	11	14	25

*One child had a partial dilatation at 30 seconds but became fully dilated on lateral traction.

Table 2 Association between anal dilatation and faecal loading in 136 patients. Values are expressed as number (%) of total

	Degree of dilatation		
	None	*Partial*	*Full*
No faecal loading, no abnormal perianal signs	76 (56)	9 (7)	5 (4)
No faecal loading, abnormal perianal signs	0	5 (4)	3 (2)
Total No with faecal loading	36 (26)	4 (3)	6 (4)
No with abnormal perianal signs	0	3 (2)	1 (1)
Degree of faecal loading:			
Grade 1	4	0	0
Grade 2	13	2	1
Grade 3	12	2	4
Grade 4	5	0	1
Grade 5	2	0	0
Grade 6	0	0	0
Total	112 (82)	13 (10)	11 (8)

Table 3 Numbers of patients with perianal redness, blueness, and veins. The figures in parentheses are percentages of the total

		Age (years)		*Fissures*		*Dilatation*	
	Total *136 (100)*	*Under 2* *53 (39)*	*Over 2* *83 (61)*	*With* *35 (26)*	*Without* *101 (74)*	*With* *24 (18)*	*Without* *112 (82)*
Redness:							
Not seen	51	13	38	11	40	8	41
Faint	52	20	32	10	42	9	43
Definite	26	14	12	8	18	5	23
Angry	7	6	1	6	1	2	5
Blueness:							
Not seen	86	35	51	18	68	12	74
Faint	24	10	14	8	16	9	15
Definite	23	7	16	8	16	3	20
Deep blue	3	1	2	1	1	0	3
Veins:							
Not seen	114	50	64	28	86	20	94
Visible	20	2	18	7	13	4	16
Prominent	2	1	1	0	2	0	2
Varicose	0	0	0	0	0	0	0

to 10 years; 16 were less than 1 year of age (46%) and 21 were under 2 years of age (60%); 22 (63%) were girls.

Most of the fissures were superficial and shallow and commonly seen only on lateral traction. In 17 patients the fissures looked fresh (active or signs of recent bleeding); in 15 the fissures were older, and in three patients both old and fresh fissures were seen. In 17 children only one fissure was found; in 10 there were two fissures, and in eight multiple fissures were seen. Anterior fissures were found in 10 patients, posterior fissures in four, both anterior and posterior fissures in two, and multiple fissures or fissures located elsewhere in 19. Eleven patients had both anal dilatation and fissures.

ANAL TAGS

Anal tags were seen in seven patients (5%) and were located either anteriorly or posteriorly in five patients. In five children small fissures were seen at the base of the tags, and in three there were fissures elsewhere as well. Only one patient had two skin tags. In two cases the mother said the tag had been present since birth.

ANAL WARTS AND PERIANAL OEDEMA

Neither anal warts nor perianal oedema were seen.

PERIANAL DISCOLORATION (TABLE 3)

The assessment was subjective but redness was associated with age under 2 years ($p=0\cdot01$) and with the presence of fissures ($p=0\cdot002$) but not dilatation ($p=0\cdot7$). Blueness on the other hand was not significantly related to age ($p=0\cdot7$) or fissures ($p=0\cdot1$), but was related to dilatation ($p=0\cdot028$). Perianal veins were more likely to be seen in children over the age of 2 ($p<0\cdot05$) but there was no correlation with fissures ($p=0\cdot6$), or dilatation ($p=1\cdot0$).

Thirty six patients (26%) had received local treatment (suppository, enema, or operative clearout) in the past, but only 12 had in the two weeks before they were examined. Four children with dilatation had received local treatment, but in all cases more than four months previously. There was no association between local treatment and either fissures or perianal discoloration.

Discussion

Some degree of anal dilatation is commonly seen in constipated children as the incidence of 18% (n=24) in this study suggests. This is in keeping with Clayden's retrospective report of 15%,[3] although our children had milder constipation, and with Stanton and Sunderland's incidence of 14% among children who were neither abused nor constipated.[5] Hobbs and Wynne found a high incidence (42%) of anal dilatation in sexually abused children with anal signs but overall their incidence of anal dilatation in abused children was 18%.[2] All their children were examined in the left lateral position for about 30 seconds. McCann *et al* reported a high incidence of anal dilatation (49%) in healthy children who had not been abused, but their mean observation period of four minutes was four times as long as the observation period in our study.[4] By 30 seconds only 15% of children had dilated anuses. All the children in the study by McCann *et al* were examined in the knee-chest position. We are unaware of any data comparing anal findings in children examined in the left lateral and the knee-chest positions.

We did not routinely measure the diameter of the dilated anus but when full dilatation was seen the maximum diameter was about 1–1·5 cm, although the diameter in partial dilatation was sometimes as small as 0·5 cm. The full dilatation reported here is larger than the lower reading of 0·5 cm given by Stanton and Sunderland.[5] In the study by McCann *et al* the anterior-posterior diameter varied from less than 0·1 cm to 2·5 cm (mean 1).[4]

Among our children with full dilatation, in whom by definition the rectum could be seen, the relatively high incidence of faecal loading (55%) suggests that the dilatation may have been mediated by the rectoanal inhibitory reflex. In other children local factors may have been responsible for the dilatation, as in the two with fissures and one with rectal prolapse. Two children (1·5% of the total) with full dilatation had no evidence of faecal retention when examined, nor were any local abnormalities found.

In children with partial dilatation, the rectum could not be seen. These patients had a relatively low incidence of faecal loading (31%) and it is possible that some centrally regulated factors have a causative role. We saw dilatation in some toddlers where the dilatation increased or decreased depending on the child's emotions during the examination. It is also possible that partial dilatation is an exaggeration of the normal relaxation of the external anal sphincter after voluntary contraction. Eight children with partial dilatation had local abnormalities but in a further five no local abnormalities were present. In a total of six children (4% of the total) no obvious cause was found for the dilatation (two full and four partial). Repeat examinations were carried out on the five children with full dilatation, and of seven of the nine with partial dilatation. None of the children with full dilatation had any dilatation two weeks later, whereas in three of the seven children with partial dilatation full dilatation was seen, but in association with faecal loading.

One third (n=8) of all dilatations noted in this study were not seen until lateral traction was applied to the buttocks, suggesting that the way in which the examination is undertaken may influence the incidence of dilatation. It is of note, however, that six of these children had either faecal loading or abnormal perianal signs. Sexual abuse can never be totally excluded, although it was not suspected in any of the 24 children with dilatation. Sexual abuse has subsequently been disclosed in one child in whom anal dilatation was not seen. This child (one of three secondary referrals) had no perianal signs and the abuse took place many years after the onset of the constipation.

We found a high incidence of anal fissures (n=35, 26%), which might be explained by the relatively high incidence of infants referred (53 (39%) were less than 2 years old). McCann *et al* found no anal fissures among their 267 normal children but it is of note that only 5% of their patients were less than 2 years old.[4] The mean age of children in our study was 3·9 years, compared with 5·4 years in Clayden's study of constipated children,[3] 5·7 years in the normal children reported by McCann *et al*,[4] and over 7 years in the sexually abused children reported by Hobbs and Wynne.[2] In the latter study anal fissures were found in 53% of 143 sexually abused children who had anal signs (23% of the full series of 337 children). Hobbs and Wynne reported that multiple anal fissures were particularly indicative of anal abuse.[2] In only six of the 35 children with fissures in our study were these found posteriorly, the site most commonly found in sexually abused children.[1] Eight children in our study had multiple anal fissures.

There appears to be an aetiological association between anal fissures and tags; five of seven patients with tags also had anal fissures. It is interesting that in two of these seven the mother said that the tag dated back to birth and certainly predated the fissure. Our 5% incidence of anal tags is lower than the 11% found in the normal children studied by McCann *et al*,[4] but is similar to the 3% found in the 337 children reported by Hobbs and Wynne.[2] Clayden recorded anal tags in 3% of his severely constipated patients (G S Clayden, personal communication).

Perianal redness was found in 62% of our patients, higher than the 41% among normal children reported by McCann *et al*[4] and the 53% found in sexually abused patients reported by Hobbs and Wynne.[2] There is a suggestion from our study that perianal redness may be associated with anal fissures and it is commoner in younger children who are still wearing nappies.

Blueness was associated with anal dilatation and veins were more common in the older children, possibly as a result of straining at stool. The swollen and inflamed perianal tissue with prominent veins reported in sexually abused children was not seen in any of our patients. Local treatment within the previous two weeks does not seem to be associated with local signs.

We conclude that full or partial dilatation may be seen in children presenting with constipation, although the incidence of anal dilatation is lower than in sexually abused children with anal signs. Only three quarters of the children with anal dilatation in our study had detectable faecal loading or perianal abnormalities. These abnormalities included fissures (commonly anterior or multiple), skin tags, and red and blue perianal discoloration. No anal warts or perianal oedema were seen. Fissures seem to be unusual in normal children, but are found in constipated and in sexually abused children. It is clear that there are no pathognomonic perianal signs in childhood constipation. Age may play a part in the incidence of some of the signs as may the technique of, and position adopted for, the examination.

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Ventilator dependency in the United Kingdom

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Abstract

There are 24 children who are currently long term ventilator dependent in the UK. Nine of these are cared for entirely at home. An additional 11 children have been long term ventilator dependent since March 1983. The prevalence of these children appears to be increasing. The financial and manpower resources needed for these children whether at home or in hospital is considerable. There are reasons to suppose that the apparent increase in prevalence will continue.

An attempt has been made to establish the prevalence and incidence of children on long term ventilation in the UK during the period March 1983 to June 1988. These children need considerable manpower and financial support. It is important to know therefore whether the prevalence is increasing by keeping a register of cases notified. This has also been helpful in putting clinicians with similar problems in touch with each other as well as providing a database for further research on the circumstances of the families and their coping ability.

Methods

All paediatricians in the UK were requested through a British Paediatric Association newsletter (March 1983) to notify children who had been on total ventilatory support for six months or more. The paediatricians were circulated again in 1987 for follow up information and for notification of further cases. At this time members of the Association of Paediatric Anaesthetists of Great Britain and Ireland were also contacted. Specific inquiries were made of special centres involved with ventilatory problems.

During the period of study it is probable that increasing numbers of children with neuromuscular disease have been offered ventilatory assistance, for example via a curasse or more lately via a closely fitting face mask, particularly at night. As the dependency needs and rehabilitation potential of these children are somewhat different it was decided not to include them in this study. Details requested included age, date of birth, diagnosis, date when ventilation started, and any additional details such as whether the management was more home or hospital based. For reasons of confidentially the child's name was not requested.

Results

During the period specified 35 children have been notified (a further three who have been notified since this period are not included). Numbers in broad diagnostic categories with sex, distribution, and age range when starting ventilation are set out in table 1. Included within the former group are six children injured usually as a pedestrian during a road traffic accident. Four of these are boys.

Incidence and prevalence of children notified to the study by calendar year are set out in table 2.

Ten children were ventilated mainly at home—including five of those with primary nocturnal hypoventilation. An additional five

Table 1 Diagnosis and numbers of children, sex, and age range

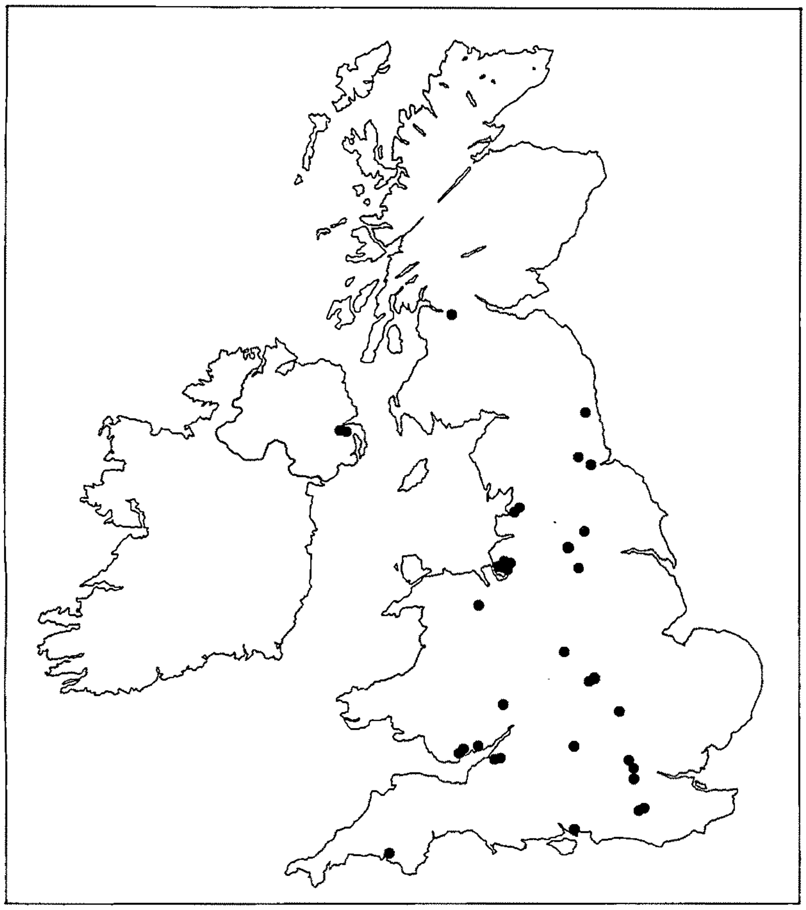
Diagnosis	*No of children*	*Boys*	*Girls*	*Age range when ventilation started*
High cervical trauma*	14	9§	4	0–12 years
Neuromuscular disease†	7	2	5	3 months–2 years
Primary nocturnal hypoventilation‡	6	2§	3	0–3 years
Infection ‖	3	2	1	2 weeks–1 year
Tumour	2	1§		6–10 years
Bronchopulmonary dysplasia	2	2		From birth
Vascular malformation	1		1	From birth

*Includes one non-accidental injury and one birth injury incurred during delivery of an extended breech.
†Consists of three with spinal muscular atrophy, three with congenital myopathy, and one with a congenital myasthenic syndrome.
‡An additional child has nocturnal hyperventilation as a sequel to herpes encephalitis and has therefore been included in the infection category.
§Sex of one of the children unknown.
‖Includes one child with poliomyelitis, one with *Haemophilus influenzae* myelitis, and one with lower brain stem herpes encephalitis.

*Table 2 Incidence and prevalence of ventilator dependent children by calendar year**

	1975	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*
Incidence	1	0	1	1	1	2	2	2	4	4	2	10	3	0
Prevalence	1	1	2	3	4	6	8	10	14	17	17	24	24	24

*Either the age or the date when starting ventilation are not available for two of the children.



Geographical distribution of ventilator dependent children in the UK during the study.

spent short periods at home. Thus 20 are or have been managed entirely in hospital—usually in intensive care units. The longest period of ventilation from childhood has been 14 years. Seventeen of the 35 have been ventilated for four years or less.

Geographical distribution is shown in the figure.

Nine children have left the register during the study period. One has left the paediatric age range, and two have been successfully weaned from the ventilator after seven and nine months; six have died. Two died from progressive deterioration of their disease, one each had aspiration pneumonia, cor pulmonale, and accidental disconnection in intensive care. One additional child died at home.

Discussion

A case finding study of this nature which is based on voluntary reporting is likely to be an underestimate, the degree of which is difficult to ascertain.

With the exception of 1986, which seems to have been an unusual year, the incidence of ventilated children would seem to have been reasonably constant during the eight years before the end of the study period. Prevalence would appear to have been rising over this time. It is possible, however, that this is an artefact of case collection. Clinicians were asked to notify children under their care at the time. As no attempt was made to collect data retrospectively it is probable that numbers of children were ventilated previously who either died or were weaned from the ventilator before this study started. Alternatively there may be a greater willingness on the part of some clinicians to embark on long term ventilation. Some support for this is given by the geographical distribution, which does not appear to follow closely centres of high population density. A number of children injured were resuscitated outside hospital. Increasing survival if real may in part be due to an increased awareness of resuscitative techniques among the general public.

Children on long term ventilation can be divided into three dependency groups. The least dependent are those children with nocturnal hypoventilation who are ambulant and ventilator independent during the day. Intermediate are those children who have chronic lung disease, who are ventilator dependent by day as well as by night, but who are less physically handicapped. The most dependent group of children have either high cervical cord disease or generalised neuromuscular disease. Although there are children in the intermediate category in the United States (A Goldberg, personal communication), none have as yet been identified in the UK.

The resources required and the stress imposed are clearly determined by the degree of dependency. It is not surprising that five of the six children with nocturnal hypoventilation are managed entirely at home.

Estimation of the financial cost of home ventilation is highly complex. It has been estimated recently in Australia that it requires a capital outlay of approximately £12 500 with an annual cost of approximately £3750.[1] This latter figure is obviously highly variable reflecting the degree of dependency and the need for professional support by the family. It is clearly important therefore that managers responsible for resource allocation need to be aware of the apparent increase in prevalence. It may be argued that funds should be made available either at regional level or from a central fund.

Increasing numbers of young men with Duchenne muscular dystrophy are on long term ventilation both in the United States and elsewhere in Europe. This issue has scarcely been addressed in the UK but may be a further cause for increased prevalence and hence resources. The ethical implications of this area are, like the financial ones, complex. In the debate it should not be forgotten, however, that one of the lessons of the poliomyelitis epidemic was that individuals totally ventilator dependent were, given a positive rehabilitation approach, able to live fulfilled lives, contributing usefully to their families as well as to society in general.

I am grateful to all the clinicians caring for these children who kindly supplied me with details of their patients.

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Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus

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Abstract

The association between infections with respiratory syncytial virus and plasma concentrations of antidiuretic hormone was assessed in 48 patients who had been admitted to hospital. The mean (SEM) concentration of antidiuretic hormone was significantly raised in patients with bronchiolitis (9·3 (1·4) ng/l) compared with non-pulmonary respiratory syncytial virus infections that cause apnoea or upper respiratory tract symptoms (6·1 (1·7) ng/l). The highest concentrations of antidiuretic hormone were seen in patients receiving mechanical ventilation (18·0 (6·7) ng/l). There were no differences in mean serum sodium concentrations among the subgroups. Hypertranslucency on chest radiograph or an arterial carbon dioxide tension above 6·67 kPa were associated with a significantly higher concentration of antidiuretic hormone. Increased or normal maintenance fluid intake in children with pulmonary respiratory syncytial virus infections may cause the same symptoms of fluid overload as the syndrome of inappropriate secretion of antidiuretic hormone. Patients with pulmonary respiratory syncytial virus infection, hypertranslucency in chest radiograph, hypercapnia, or mechanical ventilation are at risk for raised concentrations of antidiuretic hormone.

Restricted fluid intake and careful monitoring of fluid balance and plasma electrolyte concentrations are therefore necessary in these patients.

Decreased renal water excretion is a feature of various pulmonary disorders including viral and bacterial pneumonia, pneumothorax, atelectasis, and acute asthmatic attacks.[1–6] Some studies have also reported increased concentrations of antidiuretic hormone.[3–5 7] Many infants admitted to hospital with respiratory syncytial virus bronchiolitis will receive intravenous fluids because of feeding difficulties as a result of dyspnoea. In cases of inappropriate secretion of antidiuretic hormone, fluid overload may lead to accumulation of fluid in the lungs, which will further increase respiratory insufficiency in respiratory syncytial virus bronchiolitis.[8 9]

The aim of this study was to relate the severity of respiratory syncytial virus infections to plasma concentrations of antidiuretic hormone to find out which patients are at risk of inappropriate secretion of antidiuretic hormone.

Patients and methods

The Sophia Children's Hospital is a tertiary referral centre, and therefore a high percentage of high risk infants and ventilated patients are included in this study.[6 10] Forty eight patients with respiratory syncytial virus infections who were admitted to hospital because of apnoea, dyspnoea, or feeding difficulties were included in this prospective study (15 October 1987 to 1 April 1988). Respiratory syncytial virus was diagnosed by the direct immunofluorescence test of nasopharyngeal secretion (Boots Cell Tech) and culture of the virus.

Age, sex, and medical history were recorded on admission. The diagnosis of bronchiolitis was based on clinical features (tachypnoea, recession, wheezing, and diffuse fine rales). Apnoea was defined as cessation of respiration for longer than 15 seconds, or a history of cessation of breathing associated with cyanosis.

No treatment known to interfere with secretion of antidiuretic hormone was given. All patients received a fluid intake that was two thirds of the normal maintenance amount.

On admission arterial carbon dioxide tension ($PaCO_2$) was measured in capillary arterial blood and antidiuretic hormone and plasma sodium concentrations were measured in venous blood.

Samples for assay of antidiuretic hormone were collected by venepuncture and centrifuged immediately; EDTA was used as the anticoagulant. The plasma was stored at −70°C until assay. Antidiuretic hormone was measured with the INCSTAR radioimmunoassay system (Stillwater, Minnesota); it was extracted from acidified EDTA plasma with OSD silica (Waters Associates) and eluted with methanol. The effluent was blow dried at 37°C with nitrogen. Extraction recovery was about 91%, and the antidiuretic hormone concentrations were not corrected for extraction loss. At concentrations of 1·2 and 10 ng/l the intra-assay and interassay coefficients of variation were 11% and 5%, and 3% and 4%, respectively. The mean normal adult value is 1·4 ng/l (reference range 0·5–4·7 ng/l).

A chest radiograph was done on admission, which was reviewed by a paediatric radiologist who had no knowledge of the diagnosis or complications.

EVALUATION OF DATA

Patients were divided into subgroups depending on the clinical diagnosis (pulmonary respiratory syncytial virus infection—that is, bronchiolitis or pneumonia, or both—and non-pulmonary respiratory syncytial virus infection—that is, apnoea or upper respiratory tract infections). Patients with neither clinical nor radiological signs of pulmonary disease were classified as non-pulmonary respiratory syncytial virus. A further subdivision based on the findings on chest radiography (normal, atelectasis or infiltrate(s), or both, or hypertranslucency) was made. Patients receiving mechanical ventilation were considered as a separate subgroup.

The Mann-Whitney U test was used to assess differences between concentrations of antidiuretic

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Table 1 Plasma antidiuretic hormone and serum sodium concentrations in 48 patients

	Patients with non-pulmonary infections (n=11)	*Patients with bronchiolitis and/or pneumonia (n=28)*	*Patients receiving mechanical ventilation (n=9)*
Plasma antidiuretic hormone (ng/l):			
Mean (SEM)	6·1 (1·7)†	9·3 (1·4)*	18·0 (6·7)
Range	1·2–21	1·0–26	2·1–69
Serum sodium (mmol/l):			
Mean (SEM)	138 (0·8)	138 (0·5)	136 (2·0)
Range	135–144	130–143	119–147

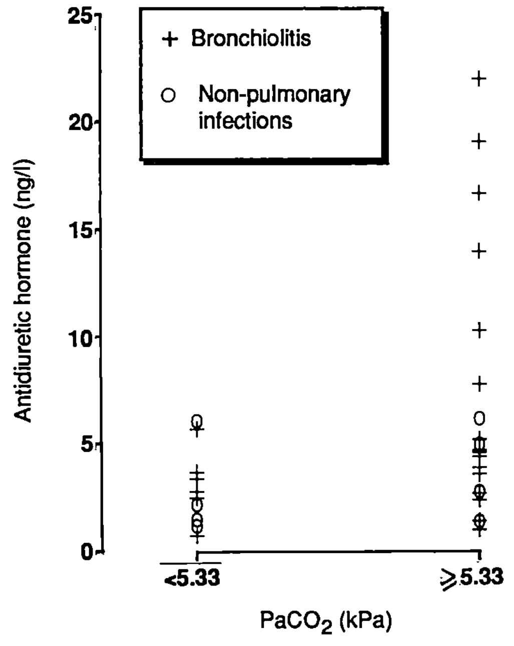
*$p<0·01$ compared with patients receiving mechanical ventilation.
†$p<0·05$ compared with patients receiving mechnical ventilation.

hormone or between plasma sodium concentrations in the different subgroups. Patients receiving mechanical ventilation were excluded from the analysis of $PaCO_2$ and chest radiographs. Approval was obtained from the institutional review board for the study. Informed consent after full information had been given was received for all patients.

Results

The median age of the patients was 104 days, and 38 (79%) were less than 1 year old on admission. The boy:girl ratio was 1·3, and a quarter were born prematurely; none had bronchopulmonary dysplasia. None of the children was clinically dehydrated on admission (loss of weight, oedema, or dry mucous membranes).

Increased plasma concentrations of antidiuretic hormone (>4·7 ng/l) were found in 27 patients (56%). In 10 patients (21%) the plasma sodium concentrations were less than 135 mmol/l on admission (reference range 135–145 mmol/l).



Association between plasma antidiuretic hormone concentrations and $PaCO_2$.

The concentrations of antidiuretic hormone were significantly raised in patients with bronchiolitis compared with patients with non-pulmonary respiratory syncytial virus infection resulting in apnoea or upper respiratory tract symptoms alone. The concentrations of antidiuretic hormone were highest in the patients receiving mechanical ventilation; the difference was significant (table 1).

The plasma sodium concentrations in patients with bronchiolitis, patients with non-pulmonary respiratory syncytial virus infection, and patients receiving mechanical ventilation were not significantly different (table 1).

The figure shows the association between $PaCO_2$ and antidiuretic hormone concentration. The number of patients with concentrations of antidiuretic hormone above 4·7 ng/l increased as the $PaCO_2$ increased. The concentration of antidiuretic hormone was increased in five of 14 patients (36%) when the $PaCO_2$ <5·33 kPa, in 11 out of 21 (52%) with a $PaCO_2$ between 5·33 and 6·53 kPa, and in all patients with a $PaCO_2$ ≥6·67 kPa. Significantly higher concentrations of antidiuretic hormone were found in patients with a $PaCO_2$ >6·67 kPa compared with patients in whom they were <5·33 kPa ($p<0·05$).

The mean plasma concentrations of antidiuretic hormone and the findings on chest radiography are shown in table 2. Hypertranslucency on the chest radiograph was associated with considerably increased concentrations of antidiuretic hormone compared with the concentrations when the radiograph was normal or showed infiltrate(s) or atelectasis, or both. There were no significant differences in plasma sodium concentrations among the subgroups, nor was any association found between findings on chest radiography and $PaCO_2$.

Discussion

The results of this study showed that patients with respiratory syncytial virus infections resulting in bronchiolitis, hypertranslucency on the chest radiograph, hypercapnia, or requiring mechanical

Table 2 Plasma antidiuretic hormone concentrations and results of chest radiography in 37 patients

	Chest radiograph		
	Normal (n=14)	*Showing atelectasis/ infiltrate(s) (n=7)*	*Showing hyperinflation (n=16)*
Plasma antidiuretic hormone (ng/l):			
Mean (SEM)	7·0 (1·5)	5·5 (2·1)	11·3 (2·0)*
Range	2·3–24	1·0–17	1–26

*$p<0·05$ compared with each of the other groups.

ventilation are at risk for increased concentrations of antidiuretic hormone. There were no significant differences in plasma sodium concentrations among the subgroups. The association between certain pulmonary processes and hyponatraemia has been known for nearly 50 years. In the 1950s the pathophysiology of hyponatraemia in pulmonary disorders was linked to inappropriate secretion of antidiuretic hormone. Since then several authors have reported hyponatraemia in association with pulmonary disorders in childhood.[1-3 5 11-13] In a few studies in children antidiuretic hormone concentrations were measured. One study reported a pronounced increase in concentrations of antidiuretic hormone during a severe asthmatic episode. No appreciable differences were found in plasma sodium concentration, plasma osmolality or urine osmolality between the asthmatic and control groups.[3] Two cases in which raised antidiuretic hormone concentrations were associated with respiratory syncytial virus bronchiolitis were reported; raised concentrations of antidiuretic hormone were also found in infants with bronchopulmonary dysplasia during periods of acute respiratory distress—all these infants suffered from hypoxaemia with air trapping.[5] Gozal *et al* have recently reported raised concentrations of antidiuretic hormone in infants with bronchiolitis of various aetiologies.[7]

Several pathophysiological mechanisms might explain our findings. The secretion of antidiuretic hormone is a homoeostatic process guided by alterations in the volume of intravascular fluid and by the osmolality of the extracellular fluid. Volume receptors are located in the left atrium, baroreceptors in the carotid arteries and the aortic arch, and osmoreceptors in the supraoptic and paraventricular nuclei of the hypothalamus. Hyperinflation of the lungs causes pulmonary hypovolaemia and decreases left atrial filling or transmural pressure of the left atrium, or both, and subsequently increases production of antidiuretic hormone.[3 5 11] It has been suggested recently that pneumonia may increase antidiuretic hormone concentrations by altering the osmoregulation of central antidiuretic hormone release so that a lower plasma osmolality is required to suppress antidiuretic hormone release fully.[4] This hypothesis explains why plasma sodium concentrations remain within the reference range in patients with raised concentrations of antidiuretic hormone.

Patients receiving mechanical ventilation have the highest plasma antidiuretic hormone concentrations; this can be explained by the severity of the pulmonary disease itself and by ventilation with positive end expiratory pressure (PEEP), which is known to increase antidiuretic hormone secretion.[12-14]

Experimental and clinical observations have suggested that hypoxaemia and hypercapnia stimulate release of antidiuretic hormone.[15] In this study a large number of patients with a $PaCO_2$ above 5·33 kPa, which can be considered as pathologically increased if tachypnoea is present, had raised antidiuretic hormone concentrations.

The increased antidiuretic hormone concentrations in pulmonary respiratory syncytial virus infections might be attributed to an interaction between osmotic control of antidiuretic hormone and a false haemodynamic signal of volume depletion. Three conditions might lead to aggravation of respiratory insufficiency in patients with respiratory syncytial virus bronchiolitis: firstly, increased negative pleural pressure in bronchiolitis might cause pulmonary fluid accumulation[16]; secondly, increased concentrations of leucotrienes were found in the nasal fluid of children with bronchiolitis,[17] and if these are also present in pulmonary tissue vascular permeability may be enhanced resulting in pulmonary fluid accumulation; and thirdly, increased or normal maintenance fluid intake in children with pulmonary respiratory syncytial virus infections will cause the clinical symptoms of fluid overload resulting from inapproriate secretion of antidiuretic hormone.

In conclusion, patients with severe pulmonary respiratory syncytial virus infections are at the risk of hyponatraemia if excessive amounts of hypotonic fluids are given. Restriction of fluid intake seems to be necessary, especially in children with severe bronchiolitis. None of the patients in this study developed inappropriate secretion of antidiuretic hormone while they were in hospital. Careful monitoring of fluid balance and plasma electrolyte concentrations is necessary to avoid a potentially harmful iatrogenic disorder.

We thank M Meradji MD, PhD, for reviewing the chest radiographs and PhH Rothbarth MD, PhD, for undertaking the virological studies.

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Effects of newborn screening of cystic fibrosis on reported maternal behaviour

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Abstract

Screening for cystic fibrosis is highly controversial. Concerns have been expressed that newborn screening may cause mothers, who had considered their child to be healthy before diagnosis, to overprotect their child. Some critics of screening also suggest that a period of delay from onset of symptoms to diagnosis may help a mother adjust to the reality of the child's lethal condition. This study compared the strength of overprotective child rearing attitudes of 29 mothers whose children were screened (13 had symptomatic children and 16 asymptomatic children) with the attitudes of 29 mothers whose children were diagnosed after the onset of symptoms. Results indicate that newborn screening had not increased a mother's tendency to overprotect her child with cystic fibrosis and in some cases the tendency had decreased. Further, delay in diagnosis when screening was not conducted usually caused mothers considerable personal distress.

Several procedures have been developed in the last two decades that identify the presence of cystic fibrosis in newborn infants. The implementation of these procedures in newborn screening programmes has been highly controversial. Not only are there disagreements about which procedure is the most acceptable, but extensive debate continues concerning the efficacy and ethics of cystic fibrosis screening for newborns.[1–15]

Speculation concerning possible negative psychological consequences of newborn screening have tended to be unspecific. In general the literature on parent-sick child relationships has focused heavily on maternal overprotectiveness.[16] The present study has therefore sought to address these broad questions from this perspective. Specifically, this study addresses the following questions:

(1) In New South Wales, does newborn screening for cystic fibrosis decrease the time from first maternal concern about cystic fibrosis related symptoms to final confirmation of diagnosis? This time span has been defined as 'diagnostic delay'.

(2) Among mothers who have become concerned by cystic fibrosis related symptoms before diagnosis ('symptomatic children'), is the length of diagnostic delay related to the strength of their maternal protectiveness?

(3) Among mothers who had not become concerned by cystic fibrosis related symptoms before diagnosis ('asymptomatic children'), what effect does absence of observable symptoms at diagnosis have upon the development of overprotective child rearing attitudes?

(4) Among mothers of asymptomatic children, is the strength of any material denial of the child's illness related to the time span from diagnosis to onset of observable symptoms (symptom delay)?

Patients and methods

SAMPLE SELECTION

Newborn screening for cystic fibrosis commenced in New South Wales in July 1981. Before this date, all first diagnoses in a family resulted from the presentation with symptoms. Since the introduction of screening all children born in this state are screened using immunoreactive trypsin assay,[17] usually within five days of birth. Assay results are usually known within 10 days of birth. If positive, a second blood sample is sought and a second immunoreactive trypsin assay is conducted, usually within three weeks of birth. Sweat tests are then conducted to confirm diagnosis. Arrangements are made for the child with cystic fibrosis to attend one of four cystic fibrosis clinics in the state.

The medical records of all children with cystic fibrosis born in New South Wales from July 1977 to March 1985 and treated at cystic fibrosis clinics showed 71 families who satisfied the following criteria:

- Only one child with cystic fibrosis in the nuclear or extended family,
- Cystic fibrosis was not immediately diagnosed at birth,
- No other familial experience of chronic or life threatening illness or accident in the child's nuclear family,
- All children in the family shared the same natural mother,
- No deaths had occurred in the child's nuclear family and none in the extended family of either parent within the last 12 months,
- Before diagnosis, parents were unaware of their possibility of having a child with cystic fibrosis.

All mothers were approached to participate in the study. Only two mothers did not reply, while five declined. During subsequent interviews, two mothers had insufficient understanding of English to participate successfully. Another mother was unable to attend because of transport delays. Between the initial approach and eventual interview, the family circumstances of three mothers changed sufficiently to disqualify them. The final study therefore involved

58 mothers, which represents 82% of the population as described above.

Mothers were divided into three groups based on their experience of the diagnostic process. The non-screened group comprised 29 mothers of children diagnosed after the onset of symptoms. All these children were born before the beginning of newborn screening.

The screened symptomatic group contained 13 mothers of screened children. These mothers had already become concerned about their child's cystic fibrosis related symptoms before both the first hint and final diagnosis of cystic fibrosis.

The screened asymptomatic group consisted of 16 mothers who did not suspect that their child was affected until the first hint of problems during the screening process.

All interviews were conducted at the mother's choice of location. Most chose their homes (n=49), some chose the cystic fibrosis clinic (n=4), and others chose the home of friends or other 'neutral' locations (n=5). All interviews lasted between one to two hours and were conducted in private.

MEASUREMENT SCALES

Three subscales of the Parental Attitude Research Inventory (PARI)[18] were used to measure protective attitudes, and one subscale was used to measure maternal denial. The PARI has been used extensively with mothers of handicapped children. The subscales 'fostering dependency', 'intrusiveness', and 'excluding outside influences' are related to constructs underlying overprotective behaviour.[16] High scores on these subscales indicate strong agreement with the overprotective sentiments. A fourth subscale, 'approval of activity', was used as a measure of maternal denial. While this subscale was not designed to measure denial, the items suggest that agreement with such sentiments as, 'Children who do not try hard for success will feel they have missed out on things later on', and, 'Parents should teach their children that the way to get ahead is to keep busy and not waste time', may indicate an unwillingness to acknowledge the more serious long term implications of the disease.

The State Trait Anxiety Inventory (STAI)[19] was also included because anxiety has also been identified as a good predictor of maternal overprotectiveness.[16]

All scales were administered only after the mother had talked extensively about her child. Each mother was asked to complete the PARI in relation to her cystic fibrosis child only.

Results

The three groups did not differ significantly on the following variables: mother's age at interview, mother's age at birth of the child, marital status, education, ethnicity, socioeconomic status, religious affiliation and practice, number of children, problems in pregnancy and birth, gestation period, number of miscarriages, and the total numbers of her supporters. The children with cystic fibrosis in each group did not differ significantly in relation to sex, birth order, birth weight, days of hospitalisation per year, and current health rating by the child's paediatrician. Birth weight and days per year of hospitalisation were taken from cystic fibrosis clinic records, and verified with mothers. Each child's paediatrician was asked to rate the current health state of the child on a 10 point likert type scale, with one equalling 'asymptomatic' and 10 equalling 'very serious'.

As expected, children in the non-screened group were significantly older than children in the two screened groups (average ages (months) were non-screened: 105·7, screened symptomatic: 30·1, and screened asymptomatic: 24·9). No significant age difference was found between the two screened groups. A systematic age difference between the non-screened and two screened groups is an inevitable, and potentially unfortunate, feature of the present design. Because of the possibility of age related effects, extensive statistical analysis was conducted within the non-screened group (the only group with a sufficient age range to give meaningful results) before finalising the research design. When partial correlation coefficients were used to control for the age of the child, no evidence was found that the child's age was influencing the associations between the dependent and independent variables. This means that the systematic age difference between the screened and non-screened groups was not influencing the results.

(1) SCREENING AND DIAGNOSTIC DELAY

Because it was obvious that the scores were skewed, log transformation was carried out on the original data. A t test was conducted on the transformed data,[20] and showed that delay in diagnosis was very much longer in the non-screened than the screened symptomatic group (t=44·60, p<0·001). The geometric means for the non-screened and screened symptomatic groups were 115·33 and 21·56 respectively. Table 1 shows the mean age of the children in the three groups and its relation to the diagnostic process.

Table 1 Mean age of child with cystic fibrosis in days at stages in the diagnostic process and number of days delay in confirmation or onset of symptoms

	Non-screened (n=29)	*Screened symptomatic (n=13)*	*Screened asymptomatic (n=16)*
First maternal concern	84	16	314
First hint of diagnoses given to mother	251	35	34
Confirmation of diagnoses given to mother	271	49	47
No of days delay from first concern to confirmation	187	33	—
No of days delay from confirmation to onset of symptoms	—	—	267

Table 2 Correlation of independent and dependent variables for non-screened group (n=29)

Category	*Anxiety state*	*Fostering dependency*	*Excluding outside influences*	*Intrusiveness*	*Birth weight*	*Child's age at first symptom*	*Delay in diagnosis*
Fostering dependency	−0·003						
Excluding outside influences	0·116	0·058					
Intrusiveness	−0·134	0·532**	0·326				
Birth weight	0·001	0·026	−0·175	−0·367*			
Child's age at 1st symptom	−0·011	−0·220	0·041	0·134	−0·149		
Delay in diagnosis	0·145	−0·338*	0·124	−0·172	−0·061	0·634**	
Current health of child	−0·063	−0·198	−0·180	0·187	−0·209	0·035	−0·085

*p<0·05, **p<0·001.

Table 3 Mean (SD) scores for protectiveness measures for each diagnostic group

	Non-screened (n=29)	*Screened symptomatic (n=13)*	*Screened asymptomatic (n=16)*	*Univariate F*	*Pooled SD*
Fostering dependency	10·79 (2·82)	8·69 (2·14)	10·25 (2·18)	3·136*	2·52
Excluding outside influences	11·07 (2·29)	11·15 (3·83)	12·06 (2·29)	0·672	2·85
Intrusiveness	10·28 (2·37)	9·38 (3·52)	12·06 (3·62)	3·055*	3·04
Anxiety state	34·93 (10·29)	34·44 (11·17)	32·44 (7·53)	0·3409	9·83

*p<0·05.

(2) DIAGNOSTIC DELAY AND MATERNAL OVERPROTECTIVENESS

Statistical analysis involved only the non-screened group because, as table 1 shows, this was the only group to experience extensive diagnostic delay. Initial analysis showed that only two independent variables were significantly related to scores on some of the four measures of maternal protectiveness. These variables were the child's birth weight, and delay in diagnosis (see table 2).

Because of the large number of correlations involved, canonical correlation analysis was used to investigate whether any one or more combinations of these independent variables were contributing to scores on the four protectiveness measures. The results were not significant (F12, 159=1·045, p>0·05), which suggests that the significant univariate correlations should be treated with some caution.

(3) ASYMPTOMATIC DIAGNOSIS AND MATERNAL OVERPROTECTIVENESS

Univariate analyses of variance (ANOVA) were conducted on the four measures of overprotectiveness and all three groups. Mean raw scores for the four measures and results of the analyses are shown in table 3.

Fostering dependency and intrusiveness were the only measures in which significant group differences were found. Mothers in the screened symptomatic group scored significantly lower on the fostering dependency scale, while mothers in the screened asymptomatic group scored significantly higher on the intrusiveness scale.

(4) SYMPTOMS DELAY AND MATERNAL DENIAL

Analysis involved only the screened asymptomatic group. The Pearson product moment correlation coefficient analysis (table 4) showed no significant association between symptom delay and scores on the 'approval of activity' subscale. There also was no significant association between the denial measure and the paediatrician's rating of the child's current health.

Table 4 Correlation coefficients for scores on approval of activity scale with delay in symptoms and current health of child (screened asymptomatic group)

Denial measure	*Delay in symptoms*	*Current health of child*
Approval of activity	0·358 (p=0·086)	0·078 (p=0·386)
Delay in symptoms	—	−0·207 (p=0·221)

Discussion

(1) SCREENING AND DIAGNOSTIC DELAY

The results indicate that in New South Wales newborn screening for cystic fibrosis considerably reduces the time between a mother's first concern for her child's cystic fibrosis related symptoms and confirmation of the diagnosis.

It has been suggested by Phelan that such reductions would only occur in communities where diagnostic procedures and infrastructures were less than ideal.[21] He suggested further that in Victoria, where screening was not then conducted, few undue delays in diagnosis occur. However, careful inquiries in several Australian states and elsewhere have shown that this is not so.[15]

(2) DIAGNOSTIC DELAY AND MATERNAL OVERPROTECTIVENESS

Among mothers of children who were not screened for cystic fibrosis, the length of delay between her first concern for the child's health and the final confirmation of diagnosis did not influence the extent to which a mother later felt anxious, wanted to exclude outside influences upon the child, or to know everything the child was thinking. As can be seen in table 2, a mother's desire to foster dependency in her child appears to decrease as length at delay in diagnosis increases. There appears to be no reasonable explanation for this significant association. However, canonical correlation analysis suggests that this apparent significance may in fact be a type I error. A long diagnostic delay did not appear to affect adversely the mother-child relationship in regard to overprotectiveness.

Even so, at least short term adverse effects on the mother from diagnostic delay became apparent during the interview. A total of 75% of mothers of non-screened children and 61% of mothers of screened symptomatic children volunteered reports of personal distress stemming from medical scepticism. Reluctance on the part of medical professionals to believe the child was sick led to responses from doctors or nurses that ranged from patronising reassurances to indignation at the mother's insistence on a second, third, or fourth opinion. It seemed that the less extreme the symptom the greater the difficulty mothers had in convincing physicians that there was a problem. Even for mothers whose children were blatantly unwell, overcoming scepticism was often not easy. Certainly the only reported long term personal ramification of these experiences was increased cynicism towards medical professionals.

(3) ASYMPTOMATIC DIAGNOSIS AND OVERPROTECTIVENESS

Anxiety state and excluding outside influence

An absence of observable symptoms at diagnosis did not appear to increase the mother's protectiveness as indicated by anxiety state, or to encourage her to discourage the influence of others on her child.

Fostering dependency

Mothers of screened symptomatic children expressed significantly less need to foster the dependency of their children by protecting them from life's difficulties and disappointments than mothers of non-screened children. The scores of mothers of screened asymptomatic children fell between these two groups.

The greater agreement of the non-screened group of mothers with these sentiments is difficult to explain, except perhaps on the basis of the inherent differences between the groups in the age of the child. However, as stated earlier, extensive statistical analysis indicated that the systematic age differences inherent in the design were not influencing the results.

An alternative explanation can be found in the mothers' own reports of their experiences. During the time before initial medical scepticism gives way to acknowledgment that the child is sick, mothers of non-screened children reported experiencing a growing sense of fear that their child's deteriorating health was the result of their own incompetence. This phenomenon has also been reported elsewhere.[22] [23]

Among the screened symptomatic group, such fears of incompetence had very little time to manifest before diagnosis exonerated the mother. However, among mothers of non-screened children, these experiences may well have instilled in the mother a greater desire to protect the child from all traumas, however mild, as a way of reassuring herself of her own competence.

The mothers of screened asymptomatic children did not have to run the gauntlet of self doubt because the child appeared healthy to everyone. However, they were in the unique position of believing that the length of time their child *remained* 'healthy' was virtually their sole responsibility, as they were the main providers of the prophylactic treatment. Why then did these mothers not express stronger needs to protect their children? Perhaps the length of time the child remains symptom free encourages maternal denial of the condition. These mothers may have been caught between two competing responses. The more effectively they protected their child from the disease, the greater the temptation to believe such protection was unwarranted.

Intrusiveness

Mean scores on the intrusiveness scale for the screened asymptomatic group were very close to those of the non-screened group. Thus absence of symptoms did not appear to increase the extent to which mothers of screened asymptomatic children felt the need to know everything their children were thinking. Mothers of the screened symptomatic children were significantly less likely than the other two groups to agree with intrusive sentiments.

It is possible in this case that age differences between the screened and non-screened groups are influencing these results. Among mothers of the older non-screened children, such a desire to know what her child is thinking may have represented a plausible technique for monitoring the child's emotional well being. Many mothers in this group voluntarily reported concern at how the child would react to learning of the long term implications of the disease.

Regardless of the extent of a mother's desire to know what her child was thinking, in the two screened groups this was not possible as the children were too young. Once again, however, for mothers of screened asymptomatic children, the pressures were different. The period of prophylactic treatment was one in which the ethos of 'always being one step ahead of trouble' may have developed to a greater extent in this group because the mother's belief that the child's continued symptom free health (and hence his longevity) was dependent upon her competence. If so, then a score on the intrusiveness scale equal to that of the non-screened group may reflect a desire to adopt such a strategy rather than reflecting its current use.

The influence of delay in confirmation on this scale is difficult to explain, especially given the comparatively short time involved. Considerable variation exists in the approach used by physicians in first mentioning cystic fibrosis to the mother, and further research, apart from clarifying the results found in this study, could examine the influences that these various approaches have on maternal attitudes.

(4) DELAY IN SYMPTOM ONSET AND MATERNAL DENIAL

Although the association between symptom delay and the extent to which mothers harbour long term ambitions for their children did not reach significance, a larger sample size may result in a significant association.

In addition, all these children received prophylactic treatment in the form of physiotherapy from the mother beginning immediately after diagnosis. It is reasonable to assume that giving this treatment helped to keep the mother more firmly 'grounded' in reality. This also may help to explain why the association between denial and symptom delay failed to reach significance. Again, further research is needed to establish the extent to which prophylactic treatment mediates this relationship.

It should also be noted that six of the seven people declining to participate in the study were mothers of screened children. While the proportion of these who considered their child to be asymptomatic at diagnosis is not known, it is possible that the sample studied may be self selecting on the basis of acceptance of the child's condition and its long term ramifications.

IMPLICATIONS OF THIS STUDY

It would seem that even in communities such as the state of New South Wales with sophisticated and well coordinated diagnostic procedures, undue delays in diagnosis occur when screening is not conducted. These delays do not appear to have had a negative effect on those aspects of the mother-child relationship measured by this study. However, medical scepticism engendered self doubt and self blame during this period, which resulted in a great deal of unnecessary distress for most mothers. In some cases this has led to persisting cynicism and mistrust of the medical profession. Thus screening of newborns, far from having detrimental effects on the mother-child relationship, has in some cases been beneficial. This is particularly true for mothers who have already become concerned for the child's health by the time of diagnosis. It would seem however, that the experiences of mothers of apparently healthy children are qualitatively different, and the possibility remains that prophylactic treatment is acting in some way to nullify any negative effects that might otherwise result.

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Central nervous system vasculitis after chickenpox—cause or coincidence?

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Abstract

A 7·5 year old boy, known to have a seizure disorder, presented with an infarct in the left middle cerebral artery territory, 10 weeks after severe chickenpox. Immunofluorescent antibody titre to the varicella zoster virus in the cerebrospinal fluid was 1:32. Cerebral angiography showed evidence of focal vasculitis. He presented again seven months later with an acute exacerbation of seizures. Magnetic resonance imaging of the brain showed an old posterior extension of the infarct, but a repeated angiography demonstrated an improvement in the vasculitic process. Cerebrospinal fluid antibody titre was again 1:32. Although this may have been an unfortunate coincidence, a possible association between chickenpox and vasculitis, similar to that reported with herpes zoster, and with potentially significant clinical implications, should be considered. As a definite proof can be obtained only by a brain biopsy, however, which is generally not indicated in such cases, only additional clinical reports can lead to delineation of this association as a definite entity.

Nervous system complications of varicella are not rare in general paediatric practice. A diversity of neurological conditions, including meningoencephalitis, acute cerebellar ataxia, and the Guillain-Barré and Reye's syndromes have been reported.[1] The varicella zoster virus may cause cerebral angiitis after herpes zoster ophthalmicus,[2] and angiitis in adults with and without immune deficiencies after other herpes zoster infections not involving the trigeminal nerve.[3–5] The association of vascular brain lesions after chickenpox, although well described,[6–9] is much less well recognised. We describe a child with cerebral vasculitis resulting in acute aphasia and hemiplegia 10 weeks after the onset of chickenpox. The dilemmas resulting from this possible association are discussed.

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Case report

A 7·5 year old boy followed up for a longstanding seizure disorder presented with acutely progressive right sided weakness and aphasia. He had weighed 2682 g at birth after an unremarkable pregnancy and delivery. His development thereafter was delayed, with a stable developmental quotient of around 70. At age 3 years he developed a mixed seizure disorder with generalised tonic-clonic seizures, partial right sided motor seizures, and drooling spells. His neurodevelopmental problems were thoroughly evaluated in another hospital, with negative results. Of note, plasma and urine amino acid pattern and magnetic resonance imaging of the brain, which were done at the age of 5·5 years, were normal. Physical and neurological examinations were unremarkable. Seizures were well controlled by the use of valproic acid, 1125 mg daily.

Chickenpox developed 10 weeks before his hemiparesis and was described as severe and widespread, with no signs of central nervous system involvement. The lesions crusted and the illness resolved after about two weeks.

Twenty four hours before his admission he was noted to have weakness in his right hand, which progressed over hours to involve the arm, after which right sided facial weakness with drooling developed, followed by inability to speak. The next day he had a right hemiplegia and expressive and receptive aphasia.

Physical examination was remarkable for numerous generalised healing chickenpox scars. He had a profound expressive aphasia, weakness of the right lower half of his face, and motor weakness (3 in a scale of 0 to 5) on the right. The deep tendon reflexes were hyperactive and his toe was 'up going' on the same side. Sensory examination was normal. His right arm and leg were mildly tremulous.

On admission his packed cell volume fraction was 0·35, white cell count $8·9\times10^9/l$ with differential count fractions of 0·08 band forms, 0·3 polymorphonuclears, 0·5 lymphocytes, 0·11 monocytes, and 0·01 atypical lymphocyte. The sedimentation rate was 6 mm in the first hour. Concentrations of serum electrolytes, results of liver function tests and determinations of anion gap, prothrombin time, and activated partial thromboplastin time gave normal results. Blood lactate concentration was 0·6 mmol/l (normal up to 3·0 mmol/l) and lactate in the cerebrospinal fluid was 1·6 mmol/l. Rheumatoid factor and anti-DNA antibodies were negative, antinuclear antibodies were positive at a titre of 1:40 (not significant below 1:160). A lumbar puncture showed normal cerebrospinal fluid pressure, normal concentrations of glucose and protein, and 1 mononuclear white blood cell/ml and 2 red blood cells/ml. The antivaricella immunofluorescent antibody titre was 1:1024 in the peripheral blood and 1:32 in the cerebrospinal fluid.

Electrocardiography and echocardiography were normal. Electroencephalography showed a consistent focal slowing over the left central parietal region, and recurrent bursts of bilateral spikes, which occasionally were more apparent over the right hemisphere.

Magnetic resonance imaging of the head (fig 1) was compatible with acute left temporal and parietal lobe infarct with an abnormal signal intensity within the left basal ganglia, compatible with lacunar infarcts. Bilateral cerebral arteriography showed long discontinuous segments of smooth, concentric narrowing, and beading involving the left anterior and predominantly the middle cerebral arteries, and some involvement of the left posterior cerebral artery (fig 2). The beading angioarchitecture of the arteries was considered to be typical of central nervous system vasculitis.

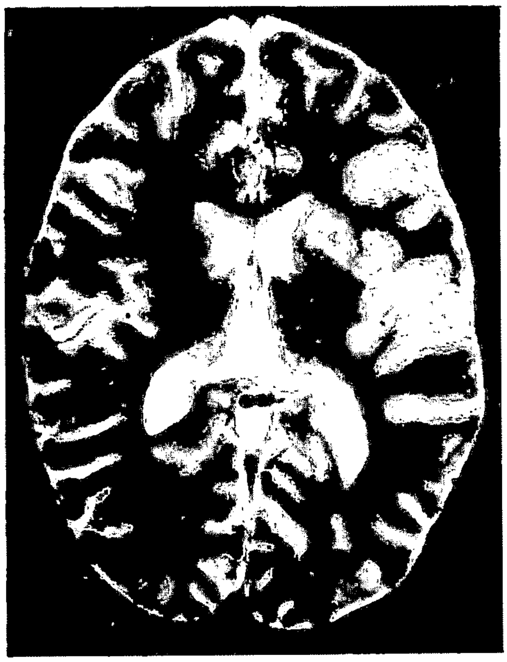

Figure 1 Magnetic resonance imaging of the brain showing the acute infarct in the left temporal and parietal lobes, with the involvement of the left basal ganglia.

In view of the vasculitic appearance of the blood vessels, steroid treatment was initiated, first with intravenous methylprednisolone for three days and then oral prednisone for a period of two months. Over several days the child showed slow but progressive clinical improvement with some return of speech and improvement of his right hemiparesis. Seizure control was also noted to be excellent, leading to a 40% decrease in the valproic acid dose three months later. The blood concentration remained within the high therapeutic range.

Seven months after the acute stroke, the child presented again with acute onset of a flurry of myoclonic seizures and aphasia, and was admitted to the hospital. At this time his packed cell volume fraction was 0·35, white cell count $7{\cdot}2\times10^9$/l, platelets 204×10^9/l, and the sedimentation rate was 6 mm/hour. Concentrations of serum electrolytes, activities of liver enzymes, and anion gap and coagulation studies were normal. Blood lactate concentration was 1·6 mmol/l. Amino acid patterns in serum and urine were normal. Rheumatoid factor, anti-DNA antibodies and antinuclear antibodies were negative, and C3 and C4 concentrations were normal. Examination of the cerebrospinal fluid showed normal concentrations of glucose and protein, 2 mononuclear white blood cells /ml and 121 red blood cells/ml. The antivaricella immuofluorescent antibody titre was 1:1024 in the peripheral blood and 1:32 in the cerebrospinal fluid.

Electroencephalography showed bilateral multifocal polyspikes, and generalised slowing of the background, which was more pronounced on the left, where the basic rhythm was decreased at times to 1–3/sec. The record suggested a diffuse encephalopathy. Magnetic

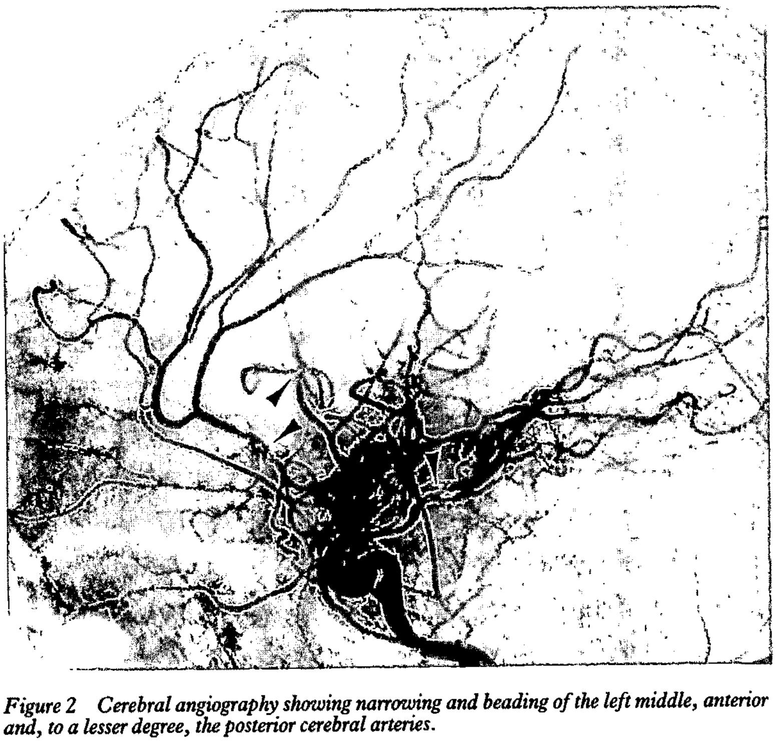

Figure 2 Cerebral angiography showing narrowing and beading of the left middle, anterior and, to a lesser degree, the posterior cerebral arteries.

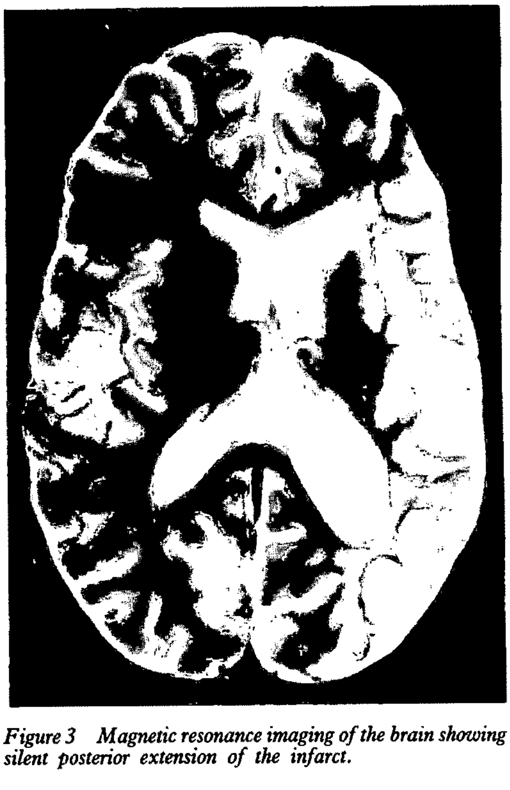

Figure 3 Magnetic resonance imaging of the brain showing silent posterior extension of the infarct.

resonance imaging of the head showed an old posterior extension of the previous infarct (fig 3). Angiography was repeated, and showed noticeable resolution of the vasculitic process, except for a residual irregularity of the proximal portion of the left posterior cerebral artery.

The seizures were controlled by increasing the valproic acid to the previous dose and adding phenytoin. When seizures were controlled, neurologic examination showed that the child was in general back to his preadmission state, with recovery of the aphasia. Drooling, as well as some degree of increased mental dullness, persisted.

Discussion

This child presented with acute onset of right hemiparesis, with changes on magnetic resonance imaging compatible with acute cerebral infarction and angiographic evidence of unilateral central nervous system vasculitis. The lack of evidence for other causes of cerebral infarcts, such as heart disease, mitochondrial angiopathy, amino acid abnormalities, hypercoagulable state, or a collagen vascular disease, together with absence of systemic disease suggest the diagnosis of a primary central nervous system vasculitis. The angiographic pattern, with segmental narrowing and beading, is compatible with granulomatous angiitis of the nervous system, a rare disorder in the paediatric age group.[2]

The association between another clinical manifestation of varicella zoster virus—the herpes zoster ophthalmicus—and delayed hemiplegia is well documented.[2] Within several weeks after the primary infection, patients with herpes zoster ophthalmicus can develop a contralateral hemiplegia, as a result of focal cerebral angiitis ipsilateral to the viral infection. Although the roentgenographic appearance of the affected vessels is similar to the cases of granulomatous angiitis of the nervous system, the two conditions differ clinically. In comparison with granulomatous angiitis of the nervous system, the herpes zoster ophthalmicus associated hemiplegia is generally less severe, is not associated with 'encephalopathic' symptoms, and is more limited in extent, and more likely to resolve.[2]

The mechanism for the vasculitis in herpes zoster ophthalmicus associated hemiplegia is unclear. Virus like particles have been reported in the cytoplasm and nuclei of smooth muscle cells from the wall of the affected vessel.[2 3 10] It has been suggested that the virus is activated in the trigeminal ganglion and spreads to the adjacent carotid artery. Some patients with herpes zoster associated cerebral angiitis have had truncal rather than trigeminal zoster eruptions. In such patients, dissemination by either a haematogenous or cerebrospinal fluid pathway must be considered.[11] Hilt *et al* demonstrated necrotising angiitis in a patient with herpes zoster ophthalmicus, but did not detect viral antigen in vessels. They suggested an immune mediated angiitis triggered by the herpes zoster as an alternate mechanism. Another patient with central nervous system vasculitis and underlying Hodgkin's disease was found to have antibodies to varicella zoster virus infection in the central nervous system without any previous vesicular eruption.[5]

The association of chickenpox and acute or delayed stroke is also documented. Griffith *et al* described a 31 year old woman who in the acute phase of chickenpox developed embolic occlusion of several cerebral arteries, due to sterile endocarditis. These authors have found more examples of chickenpox associated acute stroke in the literature.[6] An additional case of a 26 year old patient who developed cerebral infarction 11 days into disseminated varicella was also reported.[7] This patient showed evidence of mild systemic alteration in immune function, which was interpreted as suggestive of vasculitis. Kamholz and Tremblay described a 6 year old girl who developed a left hemiparesis six weeks after the onset of chickenpox.[9] A computed tomogram showed hypodensity in the region of the right basal ganglia and small areas of enhancement in the right centrum semiovale. Arteriography showed stenosis of the proximal middle and anterior cerebral arteries with distal occlusions in both territories. The authors suggested that corneal inoculation could have resulted in contiguous spread of the virus to the internal carotid artery branches. Eda *et al* described four children (age range 1 to 5 years) with acute hemiplegia and lacunar infarcts that occurred one to three months after chickenpox.[8] They failed, however, to demonstrate vasculitis in their patients.

The presumed association of varicella and vasculitis rests mainly on this temporal occurrence. The findings in the cerebrospinal fluid are not pathognomonic and may range from totally normal to a mild monocytic pleocytosis and a raised protein concentration. The presence of detectable varicella zoster antibodies in the cerebrospinal fluid (in a titre of 1:2 or greater) closely correlates with central nervous system infection with the virus, and is not found in infected patients without brain involvement.[12] Nevertheless, this finding does not directly relate the vascular findings to the infection. Definite proof of this linkage can only be obtained by cerebral biopsy, which is not indicated in our patient.

Our patient's symptoms are similar to those of the five previously reported children, with the additional radiographic demonstration of unilateral angiitis resembling that reported in both granulomatous angiitis of the nervous system and after herpes zoster ophthalmicus. Antibody production within the central nervous system was suggested by a raised cerebrospinal fluid: serum antibody ratio (1:30). We speculate that during a process of generalised dissemination in the central nervous system, the virus was able to invade the wall of blood vessels, causing angiitis.

The subsequent course of our patient was not benign. Although the arteriography showed that the vasculitic process had improved, there was a silent extension of the infarct. Moreover, it may not be excluded that the presence of antibodies in the cerebrospinal fluid in an unchanged titre, represents a reactivation of the virus. Furthermore this reactivation could be the cause of the child's new onset of seizures and the evidence on electroencephalography of a diffuse encephalopathy.

The possible association between the delayed hemiplegia and chickenpox is clinically important. A large number of management related questions remain unanswered. If this disease entity carries a relatively good prognosis, steroids may not be needed. Indeed, because of a possible reactivation of the virus, steroids might be contraindicated and acyclovir would be indicated instead. The natural history of the vasculitis, and the possibility of recurrence of a thrombotic event, necessitating immunosuppressive or antiviral or antithrombotic treatment, are unknown.

It is possible that the acute vasculitis 10 weeks after chickenpox was an unfortunate coincidence. If so, it is an interesting coincidence. We suggest that, in the future, physicians treating acute strokes in children should carefully ask about a history of antecedent chickenpox, and proceed with an appropriate evaluation.

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Reproducibility of 24 hour oesophageal pH studies in infants

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Abstract

Thirteen infants who had undergone 24 hour oesophageal pH monitoring to diagnose gastro-oesophageal reflux had a second study carried out to see if the results were reproducible. The studies were done without restricting the babies' activities. Appreciable differences were found, the percentage of the total time during which the pH was less than 4 varying by up to 3·7-fold between the two tests. The differences were largely the result of biological rather than technical variability. From these results estimates were made of the reliability of a single diagnostic study and the size of changes that would be necessary to show the effect of treatment.

These findings have a considerable impact on the diagnosis of abnormal gastro-oesophageal reflux and its response to treatment whether using 24 hour pH monitoring or any other method of measurement.

The number of different techniques for investigating gastro-oesophageal reflux indicates that none is perfect. Twenty four hour oesophageal pH monitoring, particularly when carried out at home, has the advantages of both a prolonged observation period and near normal conditions. It also has the potential disadvantages that it cannot measure the volume of refluxed material or detect any non-acidic reflux.

It has been accepted that individual subjects may have some investigations that show that gastro-oesophageal reflux is present and some that do not,[1–8] but this is usually ascribed to variations in the accuracy of the tests rather than the possibility of the same test showing reflux one day and not another. As symptoms of gastro-oesophageal reflux vary from day to day such a difference would not be surprising.

Twenty four hour pH studies cause relatively little discomfort or disruption to routine, and so are amenable to repetition to investigate their reproducibility. The results derived from pH monitoring are often subjected to detailed analysis and statistical comparisons, as opposed to simple grading as used for other methods of investigation. This makes it even more important that the reproducibility of the results is known, but there are little published data in adults and none at all in infants.[9–11]

The aim of this study was to obtain this information and use it to establish the reliability of a single normal or abnormal result in the diagnosis of gastro-oesophageal reflux and then to determine how helpful pH studies are when used to compare groups or to monitor the response of gastro-oesophageal reflux to treatment.

Patients and methods

As part of several larger studies approved by the local ethics committee pH studies were being undertaken to assess the incidence of gastro-oesophageal reflux in infants presenting with a variety of problems. Infants studied included those presenting with chronic respiratory symptoms and acute events such as choking or apnoea as well as those with vomiting. Patients were selected for the duplicate study when it would cause no extra inconvenience to the baby or to the family or an unnecessary hospital stay. Eleven infants needed to stay in hospital for a series of investigations and had their studies on consecutive days so that leaving the pH electrode in position caused no additional discomfort. The other two infants had their studies repeated because of symptoms that persisted after four and six weeks. Four infants were on antireflux treatment, which was constant throughout. No restriction was placed on the positioning or handling of the babies or on their diet. The timing and nature of their intake of food and drink were recorded.

Acceptable duplicate studies lasting at least 15 hours and including both day and night were obtained in 13 infants with ages ranging from 7 days to 11 months (median 2 months) (table 1). No results had to be discarded because of too large a drift in the electrode reading in buffer, or because the infant removed the probe too soon. One infant who would have been studied twice pulled the probe out after the first study and it was not replaced.

pH MEASUREMENTS

The Synectics ambulatory system with semi-disposable monocrystant antimony pH elec-

Table 1 Details of infants

Age	*Presenting problem*	*History of vomiting*	*Receiving treatment*
11 Days	Apnoea	No	No
5 Months	Apnoea	Yes	Yes
6 Months	Apnoea	Yes	No
3 Weeks	Apnoea	Yes	Yes
3 Months	Apnoea (preterm)	Yes	Yes
8 Months	Apnoea	Yes	Yes
2 Weeks	Apnoea	Yes	No
1 Month	Respiratory (preterm)	Yes	No
2 Months	Apnoea	Yes	No
11 Months	Failure to thrive	Yes	No
7 Days	Apnoea	No	No
2 Months	Respiratory	Yes	No
2 Weeks	Apnoea	Yes	No

trodes with an external diameter of 2·1 mm was used. Each electrode was tested in Synectics buffers of pH 7 and 1 before and after the studies to ensure that the readings did not differ by more than 0·2 pH units. The electrodes were positioned in the middle third of the oesophagus as calculated from the infants' length and confirmed on chest radiograph. A silver/silver chloride reference electrode with Hellige electrode gel was placed on the chest. The pH was recorded every four seconds in a Digitrapper Mark 11 (Synectics) before being transferred to an Amstrad PC1512. Data analysis was done with dedicated software, 'EsopHogram' (Gastrosoft Inc).

DATA ANALYSIS

The time studied was divided in different ways to give six time periods for analysis: the total time, the time excluding mealtimes, time less than or greater than two hours after a meal, and night and day. Night was arbitrarily defined as 2200 to 0600 hours. For each time period data were analysed using pH <4 to define four measures of reflux: the number of episodes, the number lasting longer than five minutes, the duration of the longest episode, and the percentage of time during which the pH was <4—also called the 'reflux index'. The number of episodes was expressed as an average rate/hour to compensate for time differences between the studies.

Table 2 Median (range) values of all results

	Firsty study	*Second study*
Original analysis		
Total time:		
No of episodes	0·99 (0·17–7·21)	0·91 (0–6·24)
No lasting >5 mins	0·13 (0–0·63)	0·10 (0–0·71)
Longest episode (mins)	40 (3–88)	15 (0–47)
Time that pH <4(%)	5·1 (1·2–25·6)	4·5 (0–21·4)
Without meals:		
No of episodes	0·97 (0·32–7·16)	0·97 (0·6–6·05)
No lasting >5 mins	0·14 (0–0·58)	0·14 (0–0·76)
Longest episode (mins)	16 (3–73)	15 (5–44)
Time that pH <4(%)	4·7 (0·9–25·9)	4·7 (2–21·6)
$\leqslant$120 Min after meal:		
No of episodes	0·88 (0–6·27)	1·21 (0·54–12·21)
No lasting >5 mins	0·09 (0–0·72)	0·08 (0–0·86)
Longest episode (mins)	8 (0–49)	7 (2–44)
Time that pH <4(%)	2·5 (0–38·5)	4·3 (0·6–39·6)
$>$120 Min after meal:		
No of episodes	0·95 (0·4–7·81)	1·15 (0·69–3·38)
No lasting >5 mins	0·10 (0–0·62)	0·20 (0–0·57)
Longest episode (mins)	11 (2–65)	13 (2–38)
Time that pH <4(%)	5·7 (0·8–21·1)	5·2 (1·0–14·4)
During the day:		
No of episodes	0·90 (0·06–8·76)	1·13 (0–9·68)
No lasting >5 mins	0·06 (0–0·75)	0·07 (0–0·94)
Longest episode (mins)	11 (0–73)	10 (0–44)
Time that pH <4(%)	2·9 (0–34·6)	4·3 (0–33·1)
During the night:		
No of episodes	0·75 (0·13–4·25)	0·63 (0–1·25)
No lasting >5 mins	0·13 (0–0·59)	0·13 (0–0·38)
Longest episode (mins)	10 (3–88)	11 (0–47)
Time that pH <4(%)	7·8 (0·7–21·5)	4·0 (0–10·2)
Using pH 4 to end reflux		
Total time:		
No of episodes	1·75 (0·65–11·93)	1·73 (0–11·04)
No lasting >5 mins	0·09 (0–0·54)	0·09 (0–0·5)
Longest episode (mins)	10 (3–49)	11 (0–36)
Time that pH <4(%)	5·1 (1·2–25·6)	4·5 (0–21·4)
$\leqslant$120 Min after meal:		
No of episodes	1·37 (0–13·37)	2·42 (0·37–19·77)
No lasting >5 mins	0 (0–0·96)	0 (0–0·69)
Longest episode (mins)	5 (0–43)	4 (2–36)
Time that pH <4(%)	2·5 (0–38·5)	4·3 (0·6–39·6)
$>$120 Min after meal:		
No of episodes	2·23 (0·53–11·23)	1·84 (0·78–7·15)
No lasting >5 mins	0·07 (0–0·64)	0·16 (0–0·57)
Longest episode (mins)	7 (2–44)	9 (0–20)
Time that pH <4(%)	5·7 (0·8–21·1)	5·2 (1–14·4)
Total time other measures		
Reflux index (pH 4)	5·1 (1·2–25·6)	4·5 (0–21·4)
Reflux index (pH 4·2/3·8)	4·6 (1·8–24·9)	4·9 (0–23·5)
Reflux index (pH 5)	24·9 (7·3–53·6)	16·9 (0–40·6)
Kaye score $<$pH 5)	30·9 (11·3–75·3)	22 (0–64·9)
Kaye score ($<$pH 4)	6·6 (1·3–39)	6·7 (0–33·7)
Area under pH 4	1·7 (0·4–17·4)	2·4 (0–13·9)
Total score	21·7 (4·7–51·9)	15·3 (3·9–41·1)

Initially the definition of the end of a reflux episode was when the pH went above 5 with its duration being the time during which the pH was less than 4. This definition is not universal,[11 12] some investigators defining the end of an episode as the point at which the pH goes above 4,[13 14] so the tests were all reanalysed using this criterion for counting episodes and measuring their duration.

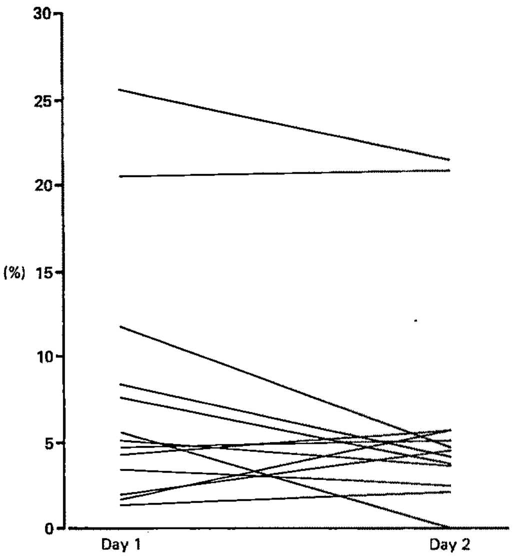
Several further variables were calculated for the total time period alone, and then compared between the two studies. The area of the curve under pH 4 was calculated by counting the number of minutes, to the nearest integer, spent between each 0·1 of a pH unit. The number of 'minute units' was calculated for each hour of study. The computer software provided a coarser definition of area (under pH 5), which was expressed as the Kaye score. This is derived by multiplying the percentage of time with pH between 4 and 5 by 1, that between pH 3 and 4 by 2, that between pH 2 and 3 by 3, and that between pH 1 and 2 by 4, and then adding them. This was also adapted to record the time that the pH was under 4 by multiplying the percentage of time with pH between 3 and 4 by 1, and so on. The percentage of the total time during which the pH was <5 was also measured. Finally, a score based on the principles of Johnson and Demeester[13 14] was calculated from the normal values in infants published by Vandenplas and Sacre-Smits.[15]

STATISTICAL METHODS

Natural logarithms of each reflux variable were taken and the difference between each of these results for each infant on the two days was calculated. A mean (SD) of the differences were thus found for each variable. By taking the antilog of 1·96 multiplied by the SD of the differences, 95% confidence intervals were calculated. Because the original results were logged these confidence intervals are expressed as the limits within which the ratio of the two results for each reflux variable for one infant should lie.

Results

Table 2 shows the medians and ranges for all the reflux variables used in the following analysis and shows no trend between the first and second studies. The reflux indices for each infant on the two occasions are illustrated in the figure. Some infants had abnormal gastro-oesophageal reflux when it was defined as a value of greater than 2SD above the mean of Vandenplas and Sacre-Smits' normal values[15] and some using a reflux index of greater than 5% (table 3). Neither method produced the same results for all infants. The mean differ-



Changes in reflux index from day 1 to day 2.

ences between the paired results for all the variables were close to zero, confirming that there was no tendency for the first or second test to give larger results.

CALCULATED RESULTS

Table 4 gives the upper confidence limits derived from the antilog of 1·96 multiplied by the SD of the logged differences; the lower limit is the inverse of this. For example, the confidence intervals for the ratio of the two reflux indices for the total time are 1/3·7 (0·27) to 3·7: that is to say that a second study will have a reflux index somewhere between 27% and 370% of the first.

TIME PERIODS

Review of the confidence intervals for all the variables showed that the total time was at least as reproducible as any other time period. Night time was the least reproducible.

REFLUX VARIABLES

The number of episodes that lasted longer than five minutes was the most reproducible measure, but several of the infants had at least some time periods during one of the studies with no such episodes. The ratio for these studies is not calculable and is excluded, possibly causing an underestimate of the variability (see table 4). The length of the longest reflux episode was the least reproducible measure in all time periods, varying up to 22-fold. The number of episodes and the reflux index have intermediate values.

Using pH 4 to define the end of the reflux episode (table 5) there was no consistent change in the confidence intervals: for some measures they increased and some decreased. This method of analysis produced more studies with no episodes lasting longer than five minutes, and so reduced the number of patients contributing to this calculation.

There is thus no apparent advantage in subdividing the total time nor in using variables other than the reflux index, which is independent of the definition of the end of a reflux episode. We therefore used this index for investigating the possible influence of electrode inaccuracies and used only the total time for further analyses.

ACCURACY OF ELECTRODES

During the testing of the pH catheters a maximum drift of pH readings in buffers of 0·2 pH units was allowed. To see whether this could be

Table 3 Results expressed as 'normal' or 'abnormal' either by Vandenplas and Sacre-Smits' results or as reflux index over 5%

	No of infants in whom both studies normal	*No of infants in whom both studies abnormal*	*No of infants in whom one study was normal and one abnormal*
Vandenplas and Sacre-Smits[15]:			
No of episodes	0	8	5
No lasting >5 mins	8	3	2
Longest episode	4	3	6
Time that pH <4(%)	4	4	5
All normal compared with any abnormal results	0	8	5
Reflux index >5%	3	2	8

Table 4 Upper limits of confidence intervals for 24 ratios. Figures in parentheses represent number of infants whose results were calculable

	No of episodes/ hour	*No of episodes/ hour lasting >5 min*	*Longest episode (min)*	*Reflux index (percentage of time that pH <4)*
Total time	3·8	2·4 (9)	11·9	3·7
Time excluding mealtimes	3·9	2·2 (8)	11·9	3·3
≤120 Min after meals	4·5	3·5 (5)	5·8	3·3
>120 Min after meals	4·4	4·3 (5)	17·1	8·5
During day (0600–2200)	5·4	4·8 (6)	8·2	5·6
During night	8·0	2·9 (6)	21·9	15·1

Table 5 Upper limits of confidence intervals after reanalysis using pH 4 to define end of reflux. Figures in parentheses represent number of infants whose results were calculable

	No of episodes/ hour	*No of episodes/ hour lasting >5 min*	*Longest episode (min)*	*Reflux index (percentage of time that pH <4)*
Total time	4·0	2·4 (6)	10·9	3·7
≤120 Min after meals	4·0	3·6 (3)	6·0	3·3
>120 Min after meals	6·3	1·4 (4)	17·1	8·5

Table 6 Upper limits of confidence intervals for all variables analysed for total time

Reflux index using pH 4 as cut off for both studies	3·7
Reflux index using pH 4·2 and 3·8 for cut off	2·9
Reflux index using pH 5 for both studies	1·9
Kaye score using pH 5 as baseline	2·0
Kaye score using pH 4 as baseline	4·4
Area under curve using pH 4 as cut off	4·9
Score for total time	3·9

responsible for some of the variability the studies were reanalysed. The study with the lower reflux index for each infant was reanalysed using a cut off value of pH 4·2 and that with the higher reflux index using a cut off of 3·8 to reduce the differences between the two studies. The confidence interval for the ratio for the reflux index for the total time was only reduced from 3·7 to 2·9-fold.

OTHER VARIABLES (table 6)
The computer software automatically calculated the Kaye score, and this result had a lower variability than the measures previously analysed. It was felt that this might be because the pattern of reflux was more accurately reflected by a measure of the 'area under the curve' so this was calculated for pH under 4. This however showed an increased variability, as did the Kaye score adapted for pH under 4. The percentage of total time during which the pH was <5 was less variable.

In case the use of a combined measure could provide a better reproducibility a score was calculated for each test using each of the four reflux variables for the total time. A result equal to the mean for the age group given by Vandenplas and Sacre-Smits scored 2 and the number of SDs away from this were added or subtracted as described by Johnson and Demeester.[13 14] The reproducibility of the total score was no better than that of any other variable.

Discussion

To investigate the reproducibility of any test, as when comparing two different methods of measurement, it is not satisfactory simply to correlate the pairs of results, as is so often done.[16] It would be surprising if there was not a correlation, because this simply means that the larger values on one occasion are likely to be larger on another. It is necessary to measure the differences between the two results, and the average of the two, and analyse these. If the differences are unrelated to the average result then they can be treated directly but if they are proportional to the average then logarithmic transformation is necessary. This transformation results in the expression of a ratio rather than an absolute difference between the results.

We used the logarithms because we found that the difference was proportional to the average for most of the reflux variables that we generated. Although not all the variables showed this pattern in our small study, the larger study of Weiner *et al* showed that the reflux index does follow this pattern and it seemed likely that all the variables would do so in a larger study.[10]

The results of reanalysing the studies at pH 3·8 and 4·2 only reduced the upper confidence limit by a fifth (3·7 to 2·9), suggesting that any variability associated with equipment was less important than biological variability. The absence of a trend for the first or second study to give higher results also militates against a deterioration in the reaction time of the electrodes. Excluding the two infants who did not have their studies on consecutive days increased the upper confidence interval for the ratio from 3·7 to 4·2.

Some investigators have used the area under the curve to reflect the intensity as well as the duration of acid exposure. Izquierdo *et al* found that this provided good discrimination between normal and abnormal reflux,[17] and Vandenplas *et al* found that it correlated better with oesophagitis.[18] In this study using the area under the curve increased the variability both when analysed accurately using 0·1 pH units and coarsely using 1 pH unit. This suggests that an increase in the time spent below pH 4 is accompanied by a proportional increase in time spent at even lower pH values. This supports our contention that minor variations in the recorded pH do not make an important contribution to the variability. It may also explain why the area under the curve provides a good discrimination, because it tends to exaggerate the differences between studies.

The use of pH 4 as a cut off value to define reflux events was initially derived on the theoretical grounds that pepsin is active at pH <4 and so oesophagitis would be likely to occur.[19 20] It was also shown that pain occurred at pH <4, although Tuttle *et al* reported that pain was caused by oesophageal distension as well as by acidity.[21] Later the use of 24 hour pH studies in subjects with and without symptoms showed that values derived using pH 4 provided the best discrimination between groups.[22 23] Some investigators disagreed, however, and found pH 5 provided a better discrimination.[24 25]

In this study the use of pH 5 as a cut off level either for the percentage of total time during which the pH was <5 or for the Kaye score representing the area of the curve under pH 5 reduced the variability. Because the area under pH 4 had a higher variability this suggested that it was the use of pH 5 rather than the use of a measure reflecting area that reduced the variability. If the use of pH 5 could also be shown to provide adequate discrimination between normal and abnormal reflux in children then it might be a more appropriate value to use.

In this study few restrictions were placed on the infants in order to study them under 'normal' conditions. It may be that for studying responses to treatment a stricter regimen would give less variability. Adult studies have, however, shown that ambulatory monitoring tends to give results that more closely reflect the clinical picture and correlate better with the presence of oesophagitis than studies carried out in hospital, so thought is needed before imposing such restrictions.[26]

This study only included infants, and the results cannot be directly extrapolated to older children. In addition the study was small and only two infants had a reflux index over 20%. Weiner *et al* studied adults with a wide range of reflux indices, however, and found that the variability was similar over the whole range with the reflux index varying up to 3·2-fold compared with 3·7 in this study.[10] Johnsson and Joelsson analysed the results differently, but if the reflux indexes are extracted from their graph and treated in the same way the result is also 3·2.[9] This suggests that until shown otherwise it may be assumed that the same conclusions apply to older children.

To derive practical information from this study the 'reliability' of a pH study and the usefulness of pH studies for comparisons were calculated using the reflux index for the total time. To estimate the 'reliability' of a normal or abnormal result the chance of getting the same answer (normal or abnormal) on a second day was calculated. Different investigators use different definitions of 'normal' but one of the values widely used to define the upper limit of normal is a reflux index of 5%. Taking this as an example it can be predicted that if a reflux index is close to 5% then there is a high chance of getting a normal result on one day and an abnormal one on another. If the patient's reflux index is less than 2·5% then there is at least a 68% chance of finding a reflux index that remains less than 5% on the second day. Similarly if the patient's reflux index is over 10% there is at least a 68% chance of a second reflux index being over 5%. If the patient's reflux index is less than 1·25% then there is virtually no chance of a second study showing a reflux index of over 5%. In the same way an original reflux index of over 20% means that a repeat study is unlikely to give a reflux index of less than 5%. This principle applies whatever value is chosen for the upper limit of the reference range. This is not the same as calculating the patient's 'true' reflux index, but because our contention is that this varies from day to day this is the best measure of 'reliability' that is possible.

When considering comparisons between groups or in individual subjects before and after treatment the pH study seems to be less useful. The extent of the variability is such that when comparing two groups it would require 80 patients/group to show an average 25% reduction in reflux index with a power of 90%. If an individual subject is treated and retested, then a 75% reduction in reflux index is necessary to be sure of a response to treatment. A lesser reduction, though seeming to be a response, might only represent the day to day variability.

CONCLUSIONS

These studies show that there was a considerable variation in the results obtained in two pH studies carried out under similar conditions in the same infants. Talking to parents indicates that their child's symptoms—at least vomiting, which is the easiest to define—vary considerably and there may be some days when it does not occur and others when it is severe. It is not surprising that the results of the pH study also varied, and it seems likely that other methods of investigating gastro-oesophageal reflux if similarly studied would also vary. We suggest that biological variability is responsible for our findings rather than any problems with the technique.

Although 24 hour pH studies provide useful information not available from other methods of investigating gastro-oesophageal reflux, the underlying variability of the amount of reflux must be taken into account when interpreting the results. If a result does not fit with the clinical picture then a repeat pH study should be considered instead of, or as well as, a different investigation. The variability that we have shown may obscure clinically important improvements in gastro-oesophageal reflux in small studies of treatment and means that new calculations for the power of such studies are needed. Forty eight hour studies would allow results to be obtained from smaller groups of patients, and even longer periods of study may be needed to provide a better picture in an individual subject.

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Indomethacin and the premature brain

Those of us who do not have a first class honours degree in physics will probably have difficulty in grasping the basic principles of near infrared spectroscopy (NIRS) and the Beer-Lambert law describing optical absorption in a highly scattering medium. Workers at the University College and Middlesex School of Medicine in London have, however, used NIRS to assess cerebral haemodynamics in premature babies given intravenous indomethacin (Edwards *et al*, *Lancet* 1990; **335**:1491–5) They found that cerebral blood flow, oxygen delivery, cerebral blood volume, and reactivity to carbon dioxide all fell sharply after giving the drug and it made no difference whether it was given rapidly or slowly. They do not, however, feel that the use of indomethacin to close patent ductus arteriosus should be abandoned but suggest that attempts should be made to ensure that oxygenation is maximal before giving the drug. That, of course, is a far from satisfactory solution, though it may be the best available at present. We badly need an alternative.

ARCHIVIST

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Bronchial asthma and acid reflux into the distal and proximal oesophagus

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Abstract

The prevalence of pathological gastro-oesophageal reflux in children and adolescents with asthma was studied by 24 hour two level oesophageal pH monitoring in 42 subjects aged 9–20 years with moderate or severe bronchial asthma. The importance of oesophagobronchial nerve reflexes and of aspiration of gastric acid as triggers in asthma was assessed by studying whether episodes of reflux into the distal and into the proximal oesophagus were followed by asthma attacks. Twenty one subjects (50%) had a pathological total reflux time in the distal oesophagus and six (16%) in the proximal oesophagus. Nine patients had pathological gastro-oesophageal reflux into the distal oesophagus together with symptoms of asthma during the day on which the recording took place. In three of them the episodes of asthma symptoms were significantly correlated with preceding episodes of reflux into the distal oesophagus, and in one subject to reflux into the proximal oesophagus.

We conclude that pathological gastro-oesophageal reflux is common in children and adolescents with asthma, but it seems to provoke symptoms of asthma in only a few. Symptoms of asthma were more often elicited by exposure of the distal oesophagus to gastric acid, possibly by a vagal reflex, than by aspiration of gastric juice.

Several studies have indicated that there is an association between gastro-oesophageal reflux and bronchial asthma in adults[1–4] and in children.[5–8] Oesophageal dysfunction is common in asthmatic children and adolescents,[9] but the prevalence of pathological gastro-oesophageal reflux is unknown.

Antireflux operations have been reported to improve asthma in subjects with severe gastro-oesophageal reflux.[10–12] Aspiration of large amounts of gastric contents can provoke severe asthma attacks, but this is probably rare.[13] Microaspiration of gastric juice has been suggested as a more frequent trigger in asthma.[14] Bronchospasm might also be caused by an oesophagobronchial nerve reflex that is elicited when the distal oesophagus is exposed to gastric acid.[15 16] The aspiration hypothesis would be supported if reflux into the proximal part of the oesophagus is shown to be followed by an attack of asthma.

Long term pH recording in the oesophagus is the most valid method of studying gastro-oesophageal reflux.[17–19] The aims of this investigation were therefore to find out the prevalence of pathological gastro-oesophageal reflux in children and adolescents with asthma by 24-hour oesophageal pH monitoring, and to study the correlation between symptoms of asthma and reflux into the distal and proximal oesophagus.

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Patients and methods

Forty two children and adolescents (25 boys and 17 girls with a mean age of 13·7 years, range 9·0–20·0) with moderate or severe asthma attending the paediatric allergy clinic were investigated by 24 hour two level pH monitoring in the oesophagus. They had all previously undergone oesophageal manometry. All patients had bronchial asthma severe enough to restrict daily activities for a total of at least 10 days during the previous year despite treatment. Eighteen patients had had symptoms of asthma during at least 100 nights or mornings during the previous 12 months.

Thirty five of the 42 subjects had atopic asthma—that is, an allergy mediated by IgE—according to the history and previous medical records. Twenty five participants (60%) had a diagnosis of oesophageal dysfunction made on manometric findings that were reported in a previous study.[9] Fourteen patients (33%) had a history of oesophageal symptoms; 13 reported acid regurgitation, seven had heartburn, and two dysphagia. None had oesophageal symptoms that required regular or current antireflux treatment.

All subjects were receiving regular treatment for their asthma. At the time of investigation oral theophylline was being taken by 23, oral β_2 adrenoreceptor stimulants by 20, inhaled β_2 adrenoreceptor stimulants by 39, sodium cromoglycate by 19, inhaled corticosteroids by 12, and oral corticosteroids by two.

24 HOUR pH TEST

For the 24 hour pH test a catheter assembly with two antimony pH electrodes was positioned with the electrodes 5 and 15 cm above the lower oesophageal sphincter. Perfused catheters with outlets 1 cm above each electrode and connected to pressure transducers permitted exact localisation of the pH probe by manometry. The catheter outlets also allowed calibration of the pH electrodes when they were in place. The overall diameter of the assembly was 3 mm. The catheter assembly was passed through the nose into the stomach. The probe was then withdrawn into the distal oesophagus and the electrodes were positioned with the participant supine. A reference electrode was attached to the chest. The pH electrodes and the reference electrode were connected to two battery operated pH meters, one for each level, and the pH signals were recorded on a portable four channel tape recorder (Oxford Medilog). The equipment was placed in a small shoulder bag so that the patients could walk freely about the ward. The electrodes were calibrated with solutions of pH 7·0 and 1·6 four times during the 24 hour period. The participants were told not to lie down during the day. During the monitoring period the subjects stayed on the paediatric ward and had a special acid free diet (pH>5) consisting of four meals. The only intake allowed between meals was medication and water. Coffee and acid drinks were not allowed. The patients took their normal treatment for asthma on the day of recording and inhaled β_2 adrenoreceptor stimulants when required.

The pH recordings were played back on a strip chart. A drop in pH to 4 or below was regarded as evidence of reflux. The percentage reflux time, the number of reflux episodes/hour, and the duration of the longest reflux episode were calculated.

In a previous study on healthy children and adolescents (14 boys and 13 girls 9·3 to 17·3 years of age, mean age 13·1 years) normal values of gastro-oesophageal reflux were evaluated by the same technique and strict standardisation as in the present investigation.[20] The upper limits of the reference ranges were defined as the upper 95th centile of percentage reflux time. Normal upper limits in the distal oesophagus were 1·0% (total reflux time), 2·0% (upright reflux time), and 0·9% (supine reflux time). In the proximal oesophagus the limits were 0·6% (total reflux time), 0·7% (upright reflux time), and 0·8% (supine reflux time).[20]

Because of disconnection of the electric cable from the proximal pH electrodes, recordings from the proximal oesophagus were not obtained in five cases.

Peak expiratory flow rate (PEFR) was checked with a Mini Wright Peak Flow Meter every hour while the patients were awake. The highest value of three was recorded on each occasion and related to the predicted PEFR.[21] The patients were given a form on which they recorded symptoms of asthma (breathlessness, wheezing, or attacks of cough), and symptoms of reflux (acid regurgitation and heartburn) and the drugs they were taking. 'Morning dipping' was defined as a decrease in the morning PEFR value by more than 20% of the mean of the other PEFR recordings.

When the association between reflux and symptoms of asthma was analysed, only reflux episodes in the distal oesophagus that lasted for at least one minute, and any episode in the proximal oesophagus that occurred within 30 minutes before the respiratory event, were considered.

STATISTICAL ANALYSIS

For statistical analysis the two tailed Mann-Whitney U test, the Fisher's exact test, the χ^2 test, and regression analysis were used. A p value of $<0\cdot05$ was regarded as significant.

ETHICS

The study was approved by the ethics committee for human research at the University Hospital, Linköping, and written consent was obtained from the participants or their parents.

Results

The total reflux time was significantly longer in the patients with asthma than in control subjects ($p<0\cdot001$, table 1). Twenty one of the 42 asthmatic children and adolescents (50%) had a pathological total reflux time (>1·0%) in the distal oesophagus. Twenty five patients (60%) had pathological reflux into the distal oesophagus either throughout the 24 hour period (n=21), or in the upright (n=15), or the supine position (n=18). Altogether 16% of the patients had patho-

Table 1 Twenty four hour two level pH monitoring in the oesophagus in 42 patients with asthma and 27 control subjects

24 hour pH monitoring	*Percentage reflux time*		*No of episodes of reflux/hour*		*Duration of longest episode of reflux (min)*	
	Asthmatic patients	*Control subjects*	*Asthmatic patients*	*Control subjects*	*Asthmatic patients*	*Control subjects*
Total period						
Distal oesophagus:						
Mean (SD)	1·52 (1·42)***	0·47 (0·39)	0·95 (0·70)***	0·43 (0·34)	5·03 (7·10)**	1·69 (1·22)
Range	0·0–5·3	0·0–1·3	0·0–2·1	0·0–1·3	0·0–8·3	0·0–5·0
Proximal oesophagus:						
Mean (SD)	0·34 (0·29)**	0·13 (0·17)	0·29 (0·27)*	0·15 (0·20)	1·39 (1·09)**	0·72 (0·97)
Range	0·0–1·3	0·0–0·6	0·0–1·0	0·0–0·8	0·0–3·5	0·0–3·3
Upright position						
Distal oesophagus						
Mean (SD)	1·82 (1·90)*	0·79 (0·73)	1·30 (1·04)*	0·76 (0·68)	2·69 (3·56)	1·43 (1·20)
Range	0·0–7·5	0·0–2·7	0·0–3·9	0·0–2·7	0·0–6·3	0·0–5·0
Proximal oesophagus						
Mean (SD)	0·36 (0·44)	0·18 (0·29)	0·36 (0·50)	0·28 (0·40)	0·95 (1·05)*	0·42 (0·57)
Range	0·0–1·5	0·0–1·2	0·0–2·6	0·0–1·7	0·0–3·5	0·0–2·3
Supine position						
Distal oesophagus						
Mean (SD)	1·18 (1·46)***	0·17 (0·33)	0·56 (0·59)***	0·08 (0·11)	3·70 (6·82)***	0·62 (1·01)
Range	0·0–6·1	0·0–1·4	0·0–2·6	0·0–2·4	0·0–8·3	0·0–3·5
Proximal oesophagus						
Mean (SD)	0·29 (0·47)*	0·10 (0·30)	0·22 (0·38)*	0·03 (0·08)	0·69 (0·91)*	0·37 (0·94)
Range	0·0–1·9	0·0–1·3	0·0–1·5	0·0–0·4	0·0–2·5	0·0–3·3

*p<0·05; **p<0·001; ***p<0·001 (Mann-Whitney U test).
Recordings in the proximal oesophagus were completed in only 37 of the 42 asthmatic patients.

Table 2 Details of nine patients with gastro-oesophageal reflux together with symptoms of asthma during the period of recording

	Case No									*Total*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
Distal oesophagus										
Total No of evaluated half hour periods	47	46	45	44	46	46	46	46	42	408
No (%) with reflux into distal oesophagus	10 (21)	10 (22)	10 (22)	14 (32)	6 (13)	7 (15)	11 (24)	5 (11)	7 (17)	80 (20)
Total No of episodes of asthma	4	6	6	5	1	3	2	1	3	31
No (%) preceded by reflux into distal oesophagus	4 (100)	3 (50)	5 (83)	5 (100)	0	1 (33)	1 (50)	0	2 (67)	21 (68)
Second proportion divided by first proportion†	4·7**	2·3	3·8**	3·2**	0	2·2	2·1	0	0	3·4***
Proximal oesophagus										
Total No of evaluated half hour periods	47	46	45	Not done	46	46	46	46	46	368
No (%) with reflux into proximal oesophagus	2 (4)	10 (22)	2 (4)	Not done	8 (17)	6 (13)	7 (15)	3 (7)	7 (15)	45 (12)
Total No of episodes of asthma	4	6	6	Not done	1	3	2	1	3	26
No (%) preceded by reflux into proximal oesophagus	1 (25)	3 (50)	2 (67)	Not done	1 (100)	1 (33)	1 (50)	0	2 (67)	11 (42)
Second proportion divided by first proportion†	5·9	2·3	7·5*	Not done	5·8	3·3	3·3	0	0	3·5***
Percentage total reflux time in distal oesophagus	2·4	2·2	5·1	4·0	2·1	2·6	4·4	1·2	1·4	2·8

*$p<0{\cdot}05$; **$p<0{\cdot}01$; ***$p<0{\cdot}001$.
†Over-representation of asthmatic episodes preceded by reflux were compared by Fisher's exact test within subjects and by χ^2 test for whole group.

logical total reflux times in the proximal oesophagus. Thirteen of the 14 patients who had histories of oesophageal symptoms had pathological gastro-oesophageal reflux.

Fifteen patients had symptoms of asthma during the day of recording. Six of these, who had 14 episodes of asthma altogether, had a normal total reflux time in the distal oesophagus. In the nine patients with both symptoms of asthma and pathological gastro-oesophageal reflux into the distal oesophagus during the recording period, there was a significant over-representation of episodes of asthmatic symptoms that were preceded by reflux into the distal oesophagus—represented by the second proportion divided by the first proportion—($\chi^2=46{\cdot}1$, df=1, $p<0{\cdot}001$), as well as into the proximal oesophagus ($\chi^2=20{\cdot}7$, df=1, $p<0{\cdot}001$); table 2). When the subjects were tested individually, three had significant correlations between episodes of reflux into the distal oesophagus and asthmatic symptoms and one between proximal reflux and asthma (table 2).

Fourteen of the 21 episodes of asthma that were preceded by reflux into the distal oesophagus, and eight of the 11 episodes that were preceded by reflux into the proximal oesophagus, were recorded when the patients were recumbent. The patients did not record any symptoms of reflux before the attacks of asthma.

Regression analysis did not show any correlation between the severity or duration of the asthma and pathological gastro-oesophageal reflux into either the distal or the proximal oesophagus, nor between the age of the patients and the severity of pathological gastrooesophageal reflux. There was no correlation between mean or morning PEFR as a percentage of the predicted value and pathological gastro-oesophageal reflux at either level of the oesophagus. There were four 'morning dippers', two of whom had completely normal 24 hour pH tests. Severity of reflux did not differ significantly between the subjects currently taking oral β_2 adrenoreceptor agonists or oral theophylline, and those not taking these drugs.

Discussion

In this study we have shown that pathological gastro-oesophageal reflux was common in children and adolescents with bronchial asthma, and in a few patients gastro-oesophageal reflux seemed to provoke symptoms of asthma. The pathological reflux was moderately severe, and the findings could even be regarded as normal if compared with the reference limits of other studies on pH monitoring.[22-26] Some of these studies can, however, be criticised for lack of standardisation,[22-24] and for the inclusion of subjects who were not in good health.[23-26] The reference range for percentage reflux time in children and adolescents referred to in our study were collected using strict criteria for normality.[20] All control subjects were admitted to hospital during the pH monitoring and were given an acid free diet, and the pH electrodes were positioned exactly 5 and 15 cm above the lower oesophageal sphincter.[20] Furthermore, the asthmatic patients in the present study and the control subjects were all investigated in the same laboratory. In healthy adults investigated in this laboratory the normal upper limit of the reference range for percentage total reflux time in the distal oesophagus was the same as in children—that is, 1·0%.[27]

A high incidence of pathological gastro-oesophageal reflux was also found by Ekström in asthmatic adults.[3] In his study, 60% of the patients had a pathological total reflux time (>1·0%). Reflux and asthma were, however, more severe and reflux symptoms were more common in the asthmatic adults than in the patients in the present study. On the other hand, only 10% of the adult asthmatic patients with pathological gastro-oesophageal reflux had attacks of asthma associated with reflux,[28] which is consistent with our findings.

The correlation between attacks of asthma and reflux into the distal oesophagus was stronger than that between asthma and reflux into the proximal oesophagus. This suggests that aspiration may be a less frequent trigger of asthma than oesophagobronchial nerve reflexes in the patients investigated. The significant correlation between reflux and episodes of asthma in the present study should be viewed with some caution. Two unrelated phenomena can have a similar pattern of occurrence, due, for instance, to a tendency to clustering in time or in periods.

The 42 subjects in the present study were recruited from a group of 55 unselected patients with moderate or severe asthma. They had previously undergone oesophageal manometry in a study aimed at investigating the incidence of oesophageal dysfunction among asthmatic children and adolescents.[9] The patients who declined to undergo 24 hour pH monitoring did not differ from the participants in the severity of their asthma, the findings at manometry, or the presence of oesophageal symptoms.

The coincidence of gastro-oesophageal reflux and asthma may have at least three explanations. Common aetiological denominators for asthma and gastro-oesophageal reflux—for example, autonomic disturbances and allergic reactions—could be one explanation. There is a high incidence of autonomic nervous system abnormalities among asthmatic subjects.[29] Furthermore, most children with asthma have some IgE mediated allergy. As inhaled antiasthmatic drugs do, to a large extent (90%), reach the gastrointestinal tract it is reasonable to believe that airborne allergens also reach the oesophagus and stomach.[30] If allergic reactions take place in the upper gastrointestinal tract they might induce hypersecretion of gastric acid or dysfunction of the oesophagus and stomach, which in turn facilitate gastro-oesophageal reflux.

Another possible explanation is that asthma or drugs for its treatment cause pathological gastro-oesophageal reflux. Ekström and Tibbling reported that reflux did not increase when bronchospasm was provoked in patients with asthma and gastro-oesophageal reflux disease[31]; on the other hand, oral theophylline increased gastro-oesophageal reflux in the same patients.[31] In the present study reflux time did not differ between those who did, and those who did not, take oral treatment for their asthma.

The third explanation is that gastro-oesophageal reflux may trigger asthmatic attacks. In spite of a high incidence of pathological gastro-oesophageal reflux in asthmatic subjects, however, reflux seems to provoke asthmatic symptoms in only a few of them. Wilson *et al* have reported that stimulation of the oesophagus by oral intake of cold or acid drinks can temporarily increase bronchial reactivity in asthmatic patients.[32] In a similar fashion, asthmatic attacks might be more easily provoked by various extraoesophageal trigger factors as a result of increased bronchial reactivity when the oesophagus is exposed to gastric juice. Additional modulating factors like recumbency and sleep might further facilitate asthmatic attacks. Hence, oesophagobronchial reflex mechanisms may be more important in asthma than has been shown in the present study.

In conclusion, moderately severe pathological gastro-oesophageal reflux is a common finding in children and adolescents with asthma. In a few of them gastro-oesophageal reflux seems to provoke episodes of asthma, probably more often through oesophagobronchial nerve reflexes induced by the exposure of the distal oesophagus to gastric acid, than by aspiration.

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Air leaks and vasopressin release

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Abstract

Eleven very low birthweight babies being ventilated for respiratory problems during the first week of life developed air leaks on 22 occasions. On 16 out of 19 occasions the infants showed increases in urinary excretion of vasopressin after these events and on 10 occasions out of 13 there was a rise in the plasma arginine vasopressin concentration. The peripheral signs of the syndrome of inappropriate antidiuretic hormone release were seen on only one occasion in response to the sometimes high vasopressin concentrations.

Air leaks are common in infants who require ventilation for respiratory problems in the first week of life. In this unit the overall incidence has been 32%, and for infants weighing less than 1000 g at birth it has been 44%, during a six year period. Management of fluid balance is also difficult in these infants. The reports of release of the antidiuretic hormone, arginine vasopressin, together with the development of air leaks[1–4] might indicate that fluid intake should be reduced after such events as is done after birth asphyxia.[5] We have evaluated 11 very low birthweight infants who developed air leaks to determine the extent to which vasopressin release occurs and to identify features suggestive of consequent fluid retention.

Patients and methods

Eleven very low birthweight infants (mean (SD) birth weight 1073 (298) g, mean (SD) gestation 27·6 (2·0) weeks) who had been included in a study to examine the control of water balance in the respiratory distress syndrome developed air leaks (pneumothorax either alone:n=7, or combined with pulmonary interstitial emphysema: n=3). A single infant developed pulmonary interstitial emphysema alone.

The infants were all nursed in air mode controlled incubators that were humidified if the infants weighed less than 1000 g (n=5). Fluid intake was standard with final adjustments on clinical grounds by the attending clinician depending on weight, electrolyte concentrations, and urine volumes. Urine was collected four hourly by the method of Liu and Anderson,[6] and the volume in the eight hours before the development of the air leak was compared with the volume passed in the following eight hours. In each four hour specimen the following were measured: osmolality (by freezing point depression), the sodium concentration (by flame photometry), and the arginine vasopressin concentration, and the values before and after the air leak were compared (table 1). Samples of plasma were taken eight hourly for measurements of osmolality and creatinine, urea, electrolyte, and plasma vasopressin concentrations. All 11 infants had severe respiratory distress syndrome and were ventilated by Bourns BP200 ventilators using standard techniques. Continuous blood pressure monitoring and transcutaneous blood gas monitoring allowed one hourly values of systolic, diastolic, and mean blood pressures and transcutaneous oxygen and carbon dioxide tensions to be averaged for the eight hours before and after the development of the air leak. Intermittent sampling of arterial blood gases was carried out, usually at intervals of three to four hours. Acid base values eight hours before and after the air leak were similarly assessed. The babies were weighed daily (usually between 4 and 6 am) and plasma and urinary vasopressin concentrations were measured by specific radioimmunoassay.[7] The study was approved by the St George's Hospital medical ethics committee.

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Results

The results are shown in tables 1 and 2.

PLASMA CREATININE

The plasma creatinine values at the time of the development of the air leak are shown in table 1. The mean concentration (103 μmol/l) is within the normal newborn reference range but infants 3, 9, 10, and 11 have values above the upper limit of this range (>120 μmol/l) indicating a degree of renal failure, though three of these infants later had values within the reference range.

PLASMA AND URINARY OSMOLALITIES

There was no significant difference (paired *t* test) between the plasma or urinary osmolalities before and after the air leaks. At both times the plasma osmolalities were high (mean (SD) before 299 (12) and after 306 (13)). The variable urine osmolalities are shown in table 1. There was no correlation between the change in the urinary or plasma osmolalities and the change in the arginine vasopressin excretion before and after the air leak.

PLASMA ARGININE VASOPRESSIN CONCENTRATION (FIG 1)

The plasma concentrations of arginine vasopressin increased after 10 of the 13 air leaks.

Table 1 Biochemical values in 11 infants before and after developing 22 air leaks correlated with urinary arginine vasopressin

Case No	*Diagnosis*	*Plasma creatinine (μmol/l)*	*Plasma osmolality (mmol/l)*			*Urinary osmolality (mmol/l)*			*Urinary volume (ml)*			*Urinary sodium (mmol/l)*			*Urinary arginine vasopressin (pmol/mmol creatinine)*		
			Before	*After*	*Difference*	*Before*	*After*	*Difference*	*Before*	*After*	*Difference*	*Before*	*After*	*Difference*	*Before*	*After*	*Differ*
1	PT	46	228	316	+28	146	155	+9	14	14	0	17	23	+6	1	1	0
	PT	68	302	—	—	260	213	−47	5	7	+2	51	11	−40	1	5	4
2	PT	98	—	306	—	84	175	+91	15	7	−8	21	26	+5	2·5	2·2	−1
3	PT	117	307	322	+15	405	387	−18	14	7 (ic)	—	70	64	−6	51	56	+4
	PT	117	307	322	+15	387	425	+38	8·5 (ic)	9·1	—	64	52	−8	—	—	
	PT	149	309	308	−1	338	398	+60	30	20	−10	126	137	+11	134	233	+99
	PT	95	309	308	−1	512	313	−200	14	9	−5	11	121	+10	127	610	+490
4	PT	103	290	310	+20	177	191	+14	40	21	−19	42	48	+6	1	1	0
5	PT	(urea 8·2)	292	302	+10	—	—	—	28	29	+1	44	58	+14	9	7	−2
	PT	(urea 7·2)	277	273	−4	—	—	—	35	16 (ic)	—	149	139	−10	40	440	+400
6	PIE	111	304	303	−1	210	386	+176	7 (ic)	48	—	58	114	+56	136	324	+178
	PT	111	303	—		386	340	−46	17	32	+15	114	125	+11	324	222	−102
7	PIE	91	313	318	+5	392	413	+21	27	28	+1	114	119	+5	22	48	+26
	PT	76	318	299	−19	182	—		38	30	−8	76	33	−43	24	99	+75
8	PIE	110	278	—	—	178	246	+68	17	21	+4	40	61	+21	25	112	+87
	PIE+PT	110	—	—	—	195	360	+165	21	27	+6	51	145	+96	112	2054	+1990
9	PT	149	286	—	—	—	—	—	9 (ic)	(ic)	—	18	—	—	3	27	+24
10	PT	130	298	—	—	269	182	−97	32	17	−15	19	27	+8	5	4·8	−0·2
	PT	93	313	—	—	241	—	—	42	(ic)	—	42	—	—	6	9	+3
11	PT	130	298	288	−10	571	553	−18	11	12	+1	144	152	+8	191	397	+208
	PT	83	288	304	+16	384	250	−134	28	14	−14	88	35	−55	189	13	−176
	PT	89	308	312	+4	416	450	+34	37	18	−19	157	169	+12	24	605	+577
Mean (SD)		103 (26)	299 (12)	306 (13)		301 (132)	320 (116)		23 (11*)	19 (8*)		73 (45)	83 (52)				
	Paired *t* test			*t*=−1·55 (p=0·2)			*t*=−0·33 (p=<0·05)			*t*=1·82 (p=0·4)			*t*=−0·74		(Wilcoxon'ssig pair test, p<0·		

Correlations between differences

r=−0·45 p=>0·1

r=+0·4 p=>0·1

r=+0·17 p=0·9

r=+0·69 p<0·01

*Only calculated on complete collections: ic=incomplete collection.
PT=pneumothorax; PIE=pulmonary interstitial emphysema.

Table 2 Plasma and urinary arginine vasopressin, body weight, plasma sodium, blood gases, and blood pressures in 11 infants before and after developing 22 air lea

Case No	*Diagnosis*	*Urinary arginine vasopressin*				*Plasma arginine vasopressin (pmol/l)*		*Weight (g)*		*Plasma sodium (mmol/)*		*Blood gases*								*Blood pressure*						*Acute hypox*
		(pmol/l)		*(pmol/4hr)*								*FiO₂ (%)*		*PaO₂ (kPa)*		*PaCO₂ (kPa)*		*pH*		*Systolic*		*Diastolic*		*Mean*		
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	
1	PT	1	1	1	4			980	1020	140	151	66	71	7·4	7·7	8·0	7·6	7·0	7·2	46	59	22	29	28	39	++
	PT	1	8	1	60	0·7	1·8	1060	980	139	139	50	40	8·9	8·8	10·3	7·3	7·12	7·24	61	55	30	33	40	42	0
2	PT	1	4	5	12	1	1	1800	1820	137	153	62	51	8·7	8·1	9·2	6·9	7·27	7·27	42	41	23	25	32	36	0
3	PT	92	84	506	714	13·3	10	975	940	142	145	41	75	7·6	6·9	4·9	7·9	7·21	7·14	50	41	29	18	34	25	+
	PT							975	940	142	145	59	76	7·6	7·4	7·9	10·6	7·14	7·01	45	44	22	20	29	28	
	PT	67	163	257	1630	13·8	46	1010	880	146	142	29	27	8	8·8	8·45	4·9	7·14	7·27	55	61	37	35	47	45	0
	PT	228	244	1368	610			880	875																	0
4	PT	1	1	15	7	1	4	1160	1820	140	147	72	77	7·7	7·9	6·78	5·77	7·23	7·24	38	48	19	20	28	30	+
5	PT	3	5	41	44	1·4	3	840	780	132	136	60	45	8·2	9	7·01	6·11	7·25	7·28	40	39	28	30	32	35	0
	PT	28	264		3168	1	2·7	780	830	136	129	?	?	9	9	7·2	11·2	7·27	7·03	44	41	34	29	39	36	++
6	PIE	122	162	329	2673			740	860	136	142	75	95	8	7·9	8·7	7·8	6·9	7·15	40	39	28	34	34	35	0
	PT	89	160	2803		1	100	740	860	136	142	94	81	8	8·3	6·8	5·6	7·22	7·28	39	41	34	36	35·5	38	0
7	PIE	20	57	280	712	5	10	1100	1095	146	146	66	90	7·1	7·6	5·1	6·3	7·3	7·2	48	50	31	35	36·5	43	0
8	PT	52	80	197	2160	4·6	3·2	1095	1070	138	144	69	71	7·6	8	5·0	6·1	7·45	7·39	45	43	34	28	42	34	+
	PIE	15	67	112	835			1140	Not weighed	135	137	68	97	6·6	7·0	6·1	7·4	7·25	7·19	40	49	21	28	29	37	++
9	PIE+PT	67	1027	837	1691	7	42	Not weighed		137	140	98	97	6·8	8·2	7·4	6·9	7·14	7·24	48	46	27	31	36	37	++
	PT	2	19	9	25			740	790	142	141	77	98	7·1	7·4	7·1	6·9	7·27	7·27	46	37	24	15	29	23	++
10	PT	15	8	152	80			1200	1130	140	139	67	79	8·5	7·5	5·19	5·16	7·3	7·3	37	47	28	36	33	40	++
	PT	5	13	90	312	110	160	1130		139	139	88	100	7·5	3·7	6·3	5·5	7·17	6·97	42	37	23	20	31	28	++
11	PT	446	873	2810	4365		2	1185	1185	140	140	46	43	7·4	7·8	7·1	7·0	7·26	7·26	Not measured					54	0
		246	13	1968	260	2	9	1185	1185	140	137	33	23	8·1	9·2	6·3	3·4	7·38	7·36	64	75	33	36	46	50	0
	PT	17	484	408	5808			1030	985	149	148	21	21	11·7	11·3	7	6	6·95	7·36	45	47	26	26	32	34	++

PT=pneumothorax; PIE=pulmonary interstitial emphysema.

The median increase of 7 pmol/l was significant ($p<0·02$, Wilcoxon's signed pair test).

URINARY ARGININE VASOPRESSIN CONCENTRATION (FIG 2)

In 17 of the 21 air leaks there was an increase in the excretion of arginine vasopressin in the four hours after the leaks. The median increase of 32 pmol/mmol creatinine was significant ($p<0·02$, Wilcoxon's signed pair test).

PLASMA SODIUM CONCENTRATION

The median change in the plasma sodium was 0 mmol/l after the 21 air leaks. The maximum fall was 7 mmol/l (from 136 to 129 mmol/l). This baby gained 50 g in weight, and this was the only occasion on which a possible effect of the secretion of arginine vasopressin was seen. The plasma arginine vasopressin concentration rose from 1 to 2·7 pmol/l, but the urinary excretion rose from 40 to 440 pmol/mmol creatinine. The baby who had a fall in plasma sodium concentration of 1 mmol/l had an increase in urinary excretion from 3 to 27 pmol/mmol creatinine, but plasma arginine vasopressin measurements were not available.

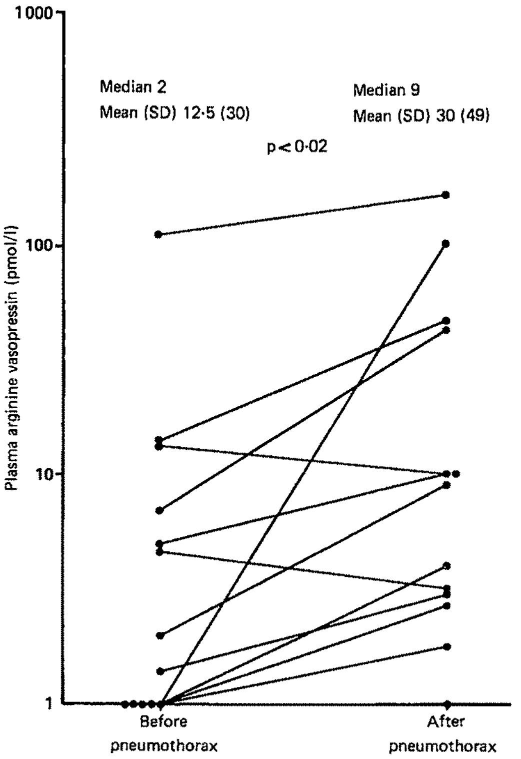

Figure 1 Plasma arginine vasopressin concentrations before and after 13 pneumothoraces or air leaks.

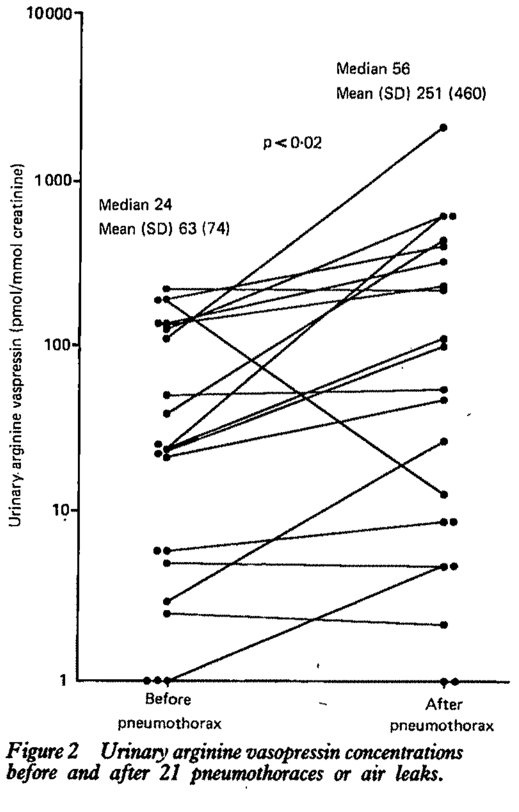

Figure 2 Urinary arginine vasopressin concentrations before and after 21 pneumothoraces or air leaks.

URINARY SODIUM CONCENTRATION

There was no significant change in the urinary sodium concentration when an air leak developed (table 1), though there was a highly significant correlation ($p < 0·01$) between the change in urinary arginine vasopressin excretion and the change in urinary sodium concentration.

URINE VOLUMES

The development of an air leak was accompanied by a significant reduction in the urine volume (23 (11) ml during the eight hours before, compared with 19 (8) ml during the eight hours after, $p < 0·05$) though the change in urine volume did not correlate with the change in urinary arginine vasopressin excretion.

WEIGHT

There was a median weight loss of 15 g (ranging from a loss of 130 g to a gain of 120 g). Three babies gained 120 g but all also had rises in plasma sodium concentrations. In only two babies was a gain in weight accompanied by a decrease in plasma sodium concentration, though in one case this was only by 1 mmol/l, which is within the range of error of the measurement.

BLOOD PRESSURE AND BLOOD GAS TENSIONS

There were no significant changes in systolic, diastolic, or mean blood pressures, or pH arterial carbon dioxide ($PaCO_2$) or oxygen (PaO_2) tensions. In 11 cases there was appreciable acute 'hypoxia' (described in the hospital notes) at the time of the development of air leak, which was rapidly corrected. These babies did not show any significant changes in blood pressure as a consequence and showed no greater increase in plasma vasopressin concentrations ('hypoxia', median increase=2·0 pmol/l, compared with 'no appreciable hypoxia', 5 pmol/l) or in the urine excretion ('hypoxia', median increase=24 pmol/mmol creatinine compared with 'no appreciable hypoxia', 11 pmol/mmol creatinine).

Discussion

In 1977 Paxson *et al* reported the syndrome of inappropriate antidiuretic hormone release after air leaks in ventilated newborns.[1] The diagnosis was made because of the development of hypo-osmolar serum in the presence of concentrated urine. Neither plasma concentrations nor urine vasopressin excretion were measured. Analysis of these patients indicated no association with hypoxaemia and there was no apparent difference in the clinical features of babies who had pneumothorax and inappropriate antidiuretic hormone release (14%) and those who did not (86%). Stern *et al* described 10 ventilated patients with acute and symptomatic pneumothorax; all had significant deterioration in PaO_2 and acid base, but none was recorded as being hypotensive.[2] Vasopressin excretion rose significantly but with successful treatment returned to normal within 8–16 hours. Only two of the infants became hyponatraemic and fulfilled the criteria for inappropriate antidiuretic hormone release. Three babies who had high and prolonged arginine vasopressin excretion did not develop hyponatraemia. Rees *et al* (1984) described one baby who had a large increase in arginine vasopressin excretion after a bilateral tension pneumothorax and the urine became concentrated. The baby was also acidotic and hypoxaemic.[3] Wiriyathian *et al*, investigating serial arginine vasopressin excretion, described four infants in whom significant increases in arginine vasopressin excretion followed a pneumothorax but no plasma concentrations were mentioned and there is no indication that these infants developed inappropriate antidiuretic hormone release.[4]

Our data are the first to examine changes in plasma vasopressin concentrations at the same time as urinary vasopressin excretion in the presence of air leaks in newborn infants. We agree that there is often a sustained excretion of vasopressin in response to the development of an air leak, but this is certainly not invariable and happened in only 15 of 21 episodes (71%). In addition, the high urinary excretion is also not always accompanied by high plasma concentrations. It is difficult to explain this unless concurrent renal damage is leading to a vasopressin leak without accumulation in the plasma, or unless the release of vasopressin has been short lived. Although four of our infants had raised plasma creatinine values, in three it was for only a short time and we believe that the release of arginine vasopressin is sometimes short lived after an air leak. In contrast, on two occasions a pronounced rise in plasma vasopressin concentration was not associated with an increase in urinary vasopressin excretion, and the correlation—considering all infants—between plasma concentration and the preceeding four hourly excretion was not significant (r=0·18, p=0·55). The babies reported in these studies all had respiratory problems and were also being ventilated, both of which factors have been associated with inappropriate antiduiretic hormone release.[8, 9]

Analysing the mechanism stimulating secretion is difficult. Paxson *et al* could not show any association with hypoxaemia and we agree.[1] Although hypoxia is a powerful stimulant of vasopressin release,[12] we are not aware of work showing that the release occurs at a particular PaO_2, either immediately or after a finite period, or whether there is an inverse linear relationship of vasopressin excretion with PaO_2 (other stimuli not contributing). None of the 11 infants recorded as being 'acutely hypoxic' in the case notes had a chronic reduction of PaO_2 before or after the events when average hourly data were examined, but the urgency with which air leaks are rectified by thoracocentesis usually means that hypoxia is short lived. This may account for the lack of difference in 'hypoxic' compared with 'non-hypoxic' infants. There was no significant change in our babies in blood gas or acid base state, and no change in mean blood pressure.

Pressure changes in the mediastinum may be transmitted to the intrathoracic baroreceptors and might be considerable when a pneumothorax develops. It might explain the high circulating concentrations of antidiuretic hormone in babies that are ventilated with positive pressure ventilation.[9, 10] Only one of our infants (case 5) showed any suggestion of inappropriate antidiuretic hormone release with a rise in body weight and a fall in plasma sodium and osmolality. The urinary sodium remained high throughout, and the episode required no treatment. It is surprising that the syndrome was not seen more often as in many cases both the plasma concentrations and the urinary excretions of vasopressin were massive. Both Wiriyathian *et al*,[4] and Rees *et al*,[3] have suggested a relative refractoriness of the neonatal kidney to the antidiuretic effects of arginine vasopressin—possibly as a result of the presence of circulating antagonists such as prostaglandin E_2.[11] This might account for our results, but no measurements were made.

A further confounding variable might be the development of intraventricular haemorrhage. Such haemorrhages are common in preterm infants with respiratory problems and air leaks and may also be associated with vasopressin secretion.[3] During the time of this study we were not carrying out repeated ultrasound scans so have no data about whether some of the high plasma concentrations and urinary excretions were associated with this problem.

The weight loss in these infants is no more than one would expect in newborn infants over the first days of life and although the plasma osmolalities were high we do not think that this was the result of dehydration because of the appropriate release of arginine vasopressin. The rise in seven osmolar points is far from significant, and there is no correlation between the osmolalities or the change in osmolality with the vasopressin release.

Overall we believe that the rises in both plasma concentration and urinary excretion of vasopressin is related to the development of the air leak, though the mechanism remains unclear and could be related to disturbed mediastinal pressure.

Of practical importance is whether fluid should be restricted after the development of an air leak in the same way as after birth asphyxia.[6] Our results suggest that such restriction should certainly not be routine. In five of the infants the increase in vasopressin with the event was <2 pmol/l, and in two of these the concentrations fell. We believe that because of the previous reports,[1–4] the urinary and plasma osmolality and the plasma sodium concentration should be monitored, but that fluid restriction should not usually be necessary.

We thank doctors and nurses in the South West Thames Regional Neonatal Intensive Care Unit for their care and cooperation, Miss Elaine Forbes for secretarial assistance, and Birthright for support of AS.

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Recognising failure to thrive in early childhood

A G K Edwards, P C Halse, J M Parkin, A J R Waterston

Abstract

The maximum weight centile achieved by a child between 4 and 8 weeks of age was found to be a better predictor of the centile at 12 months than the birth weight centile. Children whose weight deviated two or more major centiles below this maximum weight centile for a month or more showed significant anthropometric differences during the second year of life from those who showed no such deviation. It is suggested that this leads to a logical and practical definition of failure to thrive.

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The term 'failure to thrive' is applied to children who fail to gain weight adequately and therefore do not achieve a normal or expected rate of growth. It is a well known concept to child health workers. The prevalence varies, but in some communities has been reported to be as high as 5–10%,[1] and it may account for 1–5% of paediatric hospital admissions under 2 years of age.[2 3] Failure to thrive may lead to delayed physical and intellectual development[4] and it may be associated with child abuse.[5 6] Important as the condition is, however, the disturbance of growth justifying the diagnosis is at present arbitrary.[7 8] Growth in infancy is usually assessed by serial weight measurements alone as, unfortunately, length is rarely recorded routinely and is difficult to measure accurately. Some authors have included children whose weight is below the 10th centile in the failure to thrive group,[9] and others have taken the third centile as the criterion.[10 11] More stringent definitions have required the child's growth trajectory to 'fall rapidly down through the centiles'[12] or that weight gain should accelerate after hospitalisation.[13–15] A logical and generally accepted definition of failure to thrive is needed and would enable potentially vulnerable children to be identified at an early age and facilitate both research and secondary preventative initiatives.

The term failure to thrive implies failure to achieve a normal rate of growth and so the criterion for diagnosis should involve sustained deviation for a defined period from the child's expected growth trajectory. This is the nub of the difficulty. There is at present no reliable method of estimating an infant's expected growth pattern and it may be impossible to do so precisely.[16] The birth weight centile is often used for this purpose but it is determined largely by maternal influences such as height, age, parity and nutrition, smoking and alcohol consumption during pregnancy, and little by the child's genotype.[17 18]

The genetic contribution to a child's weight is greater by the age of 4–8 weeks,[19] by which time most children undergo a routine medical examination. Most 'catch up growth' in light for dates babies has taken place by this age, although 'catch down growth' is characteristically slower.[19] For this study we therefore examined first whether the maximum weight centile between 4 and 8 weeks of age was a better predictor of the future growth trajectory than the birth weight centile. We then tested this hypothesis in a population in which failure to thrive was common.

Patients, methods, and results

BIRTH WEIGHT OR WEIGHT AT 4 TO 8 WEEKS AS PREDICTOR

The weight records of two groups of singleton children aged 12–24 months from Newcastle upon Tyne and south Devon were examined. Of the 78 children in a general practice in south Devon 66 had weight measurements plotted on Sheffield charts at birth, 4–8 weeks, and 9 months, and 43 at birth, 4–8 weeks, and 12 months. 160 children attended two child health clinics in Newcastle for their surveillance. Of these 129 had weights recorded at birth, 4–8 weeks, and 9 months, and 108 at birth, 4–8 weeks, and 12 months, plotted on the Gairdner–Pearson charts,[20] which are very similar to the Sheffield charts.[21] The weight centiles at birth and at 4–8 weeks were compared with those at 9 or 12 months of age for each child. 'Deviation' between the earlier and later weights was defined as a weight that crossed two or more major centiles (third, 10th, 25th, 50th, 75th, 90th, and 97th centiles which are equidistant, each about 0·7 of a standard deviation apart from the next). Any change less than this, including a consistent growth pattern was regarded as 'agreement'. The results given in table 1 indicate that in both groups there was a trend towards the agreement between birth

Table 1 Agreement between weight centiles

	Total No	*No (%) agreeing at birth*	*No (%) agreeing at 4–8 weeks maximum*
Newcastle:			
Age 9 months	129	98 (76)	109 (84)
Age 12 months	108	69 (64)	82 (76)
Devon:			
Age 9 months	66	55 (83)	56 (85)
Age 12 months	43	32 (74)	37 (86)
Total:			
Age 9 months	195	153 (78)	165 (85) NS
Age 12 months	151	101 (67)	119 (79) $p<0{\cdot}05$

weight and weight at 9 or 12 months being less frequent than that between the weight centile at 4–8 weeks and later weight. This difference was significant in the combined group ($p<0·05$).

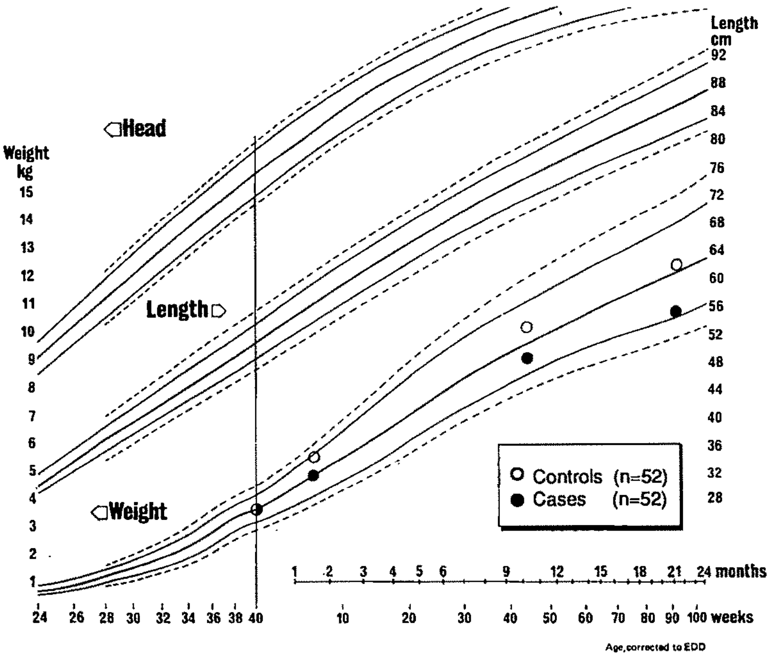
A DEFINITION OF FAILURE TO THRIVE

These findings, combined with a period of sustained reduced growth velocity, suggest a logical definition of failure to thrive: 'A child whose weight deviates downwards across two or more major centiles from the maximum centile achieved at 4 to 8 weeks for a period of a month or more'.

In order to test the validity of this definition, a group of 63 children fulfilling it at any stage during the first two years of life were identified from the weight records of 306 children attending two child health clinics and general practitioner clinics in a deprived part of Newcastle. The poor growth of five of the 63 children with failure to thrive was attributed to organic disease. Of the remaining 58 children, with non-organic failure to thrive, 52 underwent further anthropometric assessment. Each was matched with a control of the same sex and age from the group of children with normal growth attending the same clinics. The mean age of the children at assessment was 20·8 months (range 15–27) and the mean difference in ages of the two groups of children at the time of measurement was four days. The difference between the mean birth weight and gestation of the children who failed to thrive (3343 g, 39·4 weeks) and those of the control children (3355 g, 39·6 weeks) was not significant. Those who had failed to thrive were lighter (10·8 kg compared with 12·3 kg, $p<0·001$), shorter (82 cm compared with 84 cm, $p<0·001$), and had smaller head circumferences (48 cm compared with 49 cm, $p<0·01$) than the control children. The mean body mass index of the children who had failed to thrive was less than that of the control group (16·1 compared with 17·4, $p<0·001$). The mean age of first 'deviation' of cases from controls on the centile chart was 8·7 months (median 9 months, range 3–17). Table 2 shows the centile differences between cases and controls which are further illustrated in the figure.

Table 2 Centile differences between cases and controls

	Cases	*Controls*
Mean birth weight (g)	3343	3355
Median birth centile	25–50th	25–50th
Median maximum centile:		
4–8 weeks	50–75th	75th
9–12 months	25th	50–75th
At assessment (mean age 20·8 months)	10–25th	50–75th



Weight centile deviations in cases and controls.

Discussion

As several different definitions of failure to thrive have been used by clinicians and research workers, it is difficult to compare published studies, and in view of the importance of failure to thrive, this is clearly undesirable. We have shown that the maximum weight at 4–8 weeks provided a better estimate of the weight centile in later infancy than did birth weight in two very different groups of children. The Newcastle children were registered at clinics in the two most deprived electoral wards in the city defined from the 1981 census data,[22] whereas the Devon children were from a more advantaged community. Despite this both groups showed similar patterns of infant weight gain. These findings should be confirmed by larger studies in future.

Using the suggested definition of failure to thrive, based on a sustained reduction in weight velocity, 20·9% of the Newcastle children had failed to thrive at some stage. In comparison with control children from the same environment they had significantly different anthropometric measurements, being not only by definition lighter, but also shorter and thinner. Thus although the definition produced a prevalence of failure to thrive that exceeds those reported in previous studies, it also seems to have identified a group of children who may be regarded as vulnerable and worthy of investigation and intervention from child health care workers. It demonstrates the value of regular weighing of children, a practice which, though regarded as important by parents, has been questioned by the Joint Working Party on Child Health Surveillance.[23] We would suggest that a minimum level of weight monitoring in infancy should include measurement at birth, at the 6 week physical check, and at times of immunisation. These measurements would provide the means for the early detection of the effects of psychosocial deprivation as shown by growth failure.

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Professor Parkin guided and stimulated this study but tragically died before publication. The other authors dedicate the work to him.

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Food for the premature brain

Although it has long been suspected that early nutritional deprivation might impair later brain function, the evidence has been inconclusive. In an important paper from Cambridge, Norwich and Sheffield, Lucas *et al* (*Lancet* 1990;335:1477–81) have shown significant differences in the development at 18 months of premature babies fed a standard 'term' milk formula or an enriched 'preterm' formula containing nearly 40% more protein, 18% more energy, and extra sodium, calcium, phosphorus, copper, zinc, vitamins D, E and K, water soluble vitamins, carnitine, and taurine.

The study was a prospective, randomised, two centre trial involving 424 babies of less than 1850 g birth weight and about 31 weeks average gestation. The groups seemed to be similar in all important respects apart from the feeding. When tested at 18 months' post-term the children who had received preterm formula did better as regards mental, motor, and social performance, the effect being most noticeable for motor development, for boys, and for small for dates babies. In a selected group of babies who had the highest intakes of the trial feeds, the prevalence of moderate developmental impairment (Bayley score <86) was halved in those given the preterm formula.

The study is continuing. In three other centres preterm formula is being compared with donor breast milk. Follow up into adult life is planned and the results of the seven to eight year follow up now in progress will be eagerly awaited.

ARCHIVIST

Use of thermographic imaging to study babies sleeping at home

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Abstract

Two 3 month old infants sleeping under different thermal conditions were found to maintain similar deep body temperatures. Thermographic imaging suggested that though the uncovered head is the main source of heat transfer, other parts of the body such as the hands may be used when necessary.

The deep body temperatures of normal 3 month old babies fall during sleep at night in a pattern that is maintained irrespective of room temperature or thermal insulation of clothing and wrapping.[1] By this age, therefore, the thermoregulatory abilities of the babies is highly efficient, but many are kept under such warm conditions that heat loss may be compromised.[2]

In this study we examined how thermoregulation is achieved by comparing measurements of body temperature and thermographic images of two babies who maintained almost identical rectal temperature patterns in different thermal environments. As thermographic images give excellent information about surface temperatures we aimed to assess the role of the exposed parts such as head and hands in thermoregulation in the home environment, which is quite different from that in the laboratory.[3]

Methods

While recording the body temperature of babies sleeping in their cots at home we have been able to make infrared thermographic recordings on a few occasions.

Babies taking part in a larger study were recruited by health visitors, and parents were informed that the purpose of the study was to investigate the body temperature of babies at home. On the evening that the recording was to take place a health visitor fitted the baby with probes that recorded rectal temperature, abdominal skin temperature, and skin temperature on the forehead. The parents then prepared the infant for bed in the usual way, and the probes were attached to a Grant Squirrell Data Logger set to log readings every minute throughout the night. A further probe recorded the temperature in the bedroom. Note was taken of the clothing and wrapping on the baby, so that a 'tog' value could be calculated, and full details of the birth and family circumstances were recorded.

An Insight Vision Systems 80S thermal imaging camera was mounted on a tripod to record the sleeping baby's head and the top part of its wrappings. The camera black level was set so that mid range colour coding corresponded to 32°C, with a span of 2°C. The images were continuously recorded on a video recorder for the first three hours after bedtime, and individual video frames were captured and printed for illustration.

Results

Body temperature was recorded and thermal imaging carried out on five babies, four of whom slept in conditions similar for ambient temperature and insulation, and who showed similar patterns of deep body temperature and thermal imaging. Case 1 is an example of these. Case 2 slept in much hotter conditions, and made a different thermogenic response.

CASE REPORTS

Case 1

This baby was born at full term weighing 3100 g, the first son of an engineer and a medical practitioner, and was breast fed. The family lived in their own semidetached house with full gas central heating. The recordings were made in April when he was 3·5 months of age. He slept in his own room with a thermostatically controlled radiator. He wore a disposable napkin, long vest, and 'Babygro' (tog count 3·2), and was placed in a cot with a thin sheet and duvet (total tog count 9·0). The room temperature was stable, and averaged 19·5°C for most of the night. During the three hours of recording he slept quietly without turning, and seemed restful and comfortable. There was no visible sweating. Figure 1 shows his rectal temperature during the night, and fig 2 shows drawings from thermographic images taken 30 minutes and two hours after bedtime, respectively. At bedtime, when his rectal temperature was above 37°C, part of his head was warm (about 33°C),

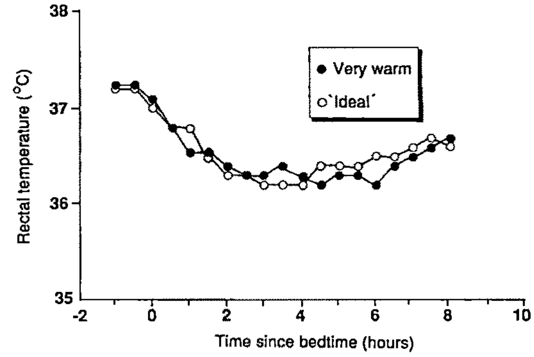

Figure 1 Rectal temperatures of case 1 (ideal) and case 2 (too warm) during the night.

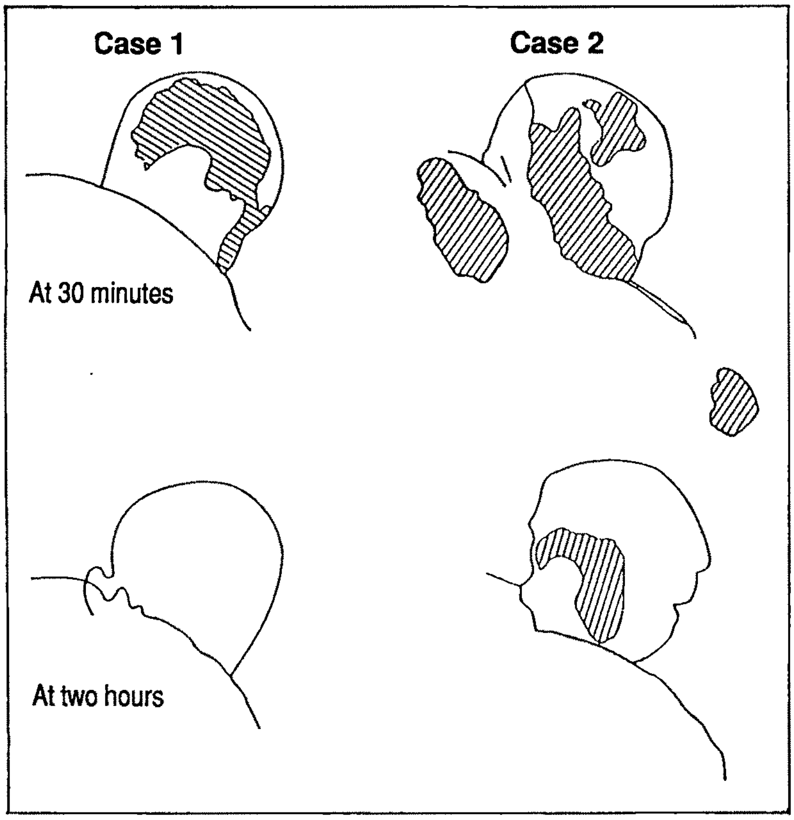

Figure 2 Thermographic images at 30 minutes and two hours after the babies had been put to bed, showing areas of maximum heat loss (shaded). Case 2 is using her hands as supplementary 'radiators'.

but as his rectal temperature fell the temperature of his head surface fell gradually by a degree or so.

Case 2

This baby was born at full term weighing 2380 g. She was the third child of young parents, and was breast fed. They lived in their own terraced house with gas central heating. Again recordings were made in April, when she was 4 months old. She slept in a cot in her parents' room, which had an uncontrolled radiator. She was dressed in a disposable napkin with plastic pants, a vest, short socks, a Babygro, and a fleecy sleep suit (total tog count 8·5). Her cot had a flannelette sheet and thermal lamb cover over the mattress, and she was covered with a flannelette blanket, and a large quilt folded into four (total tog count 20). When placed in the cot her hands were covered and the wrappings pulled well up to her head. The room temperature was 25·2°C at bedtime, and averaged 23·6°C during the three hours of thermal imaging, cooling only slightly for the rest of the night.

During the three hours of recording she was restless, and within 20 minutes had moved to expose more of her head, and removed her hands from the covers. She was obviously sweating profusely on the forehead and face. Figure 1 shows her rectal temperature during the night, which was indistinguishable from that of case 1. Figure 2 shows her thermographic images at 30 minutes and two hours after bedtime, respectively. Her head and hands remained warm throughout with the surface thermistor registering 33°C, and as she moved around she was continually exposing different parts of her head. After three hours, when her rectal temperature had cooled to 36·3°C she withdrew her hands, and her head cooled a little, though it remained much hotter than that of case 1. Both babies had the same head temperature at bedtime. Neither baby woke or cried during the time of recording, though case 2 did wake later in the night.

Discussion

These cases are a testament to the capabilities of infants for thermoregulation, and the possibility of using thermographic imaging at home to show heat loss and sleeping body movements in different home conditions. Case 1 was kept in what many would believe to be a near perfect thermal environment, lightly wrapped at 19°C. Case 2 would be described as 'over wrapped' by most observers, and slept in a decidedly warm room. Their night time patterns of rectal temperature were, however, identical and corresponded very closely to the normal pattern we have described previously.[1]

Whatever assumptions are made, it is difficult to see how case 2 could be losing any appreciable amount of heat from her heavily insulated body, and indeed her abdominal skin temperature and rectal temperature was almost identical, suggesting minimal heat flux. By some means, therefore, she lost sufficient heat through her head and hands to cool normally during sleep. This was achieved in part by increasing the exposed area as she moved around, which may indicate a considerable role for behaviour in infant thermoregulation. She was also sweating profusely, and the head and particularly hand surface temperatures were high, suggesting a considerable heat flux that was presumably attributable to increased cutaneous perfusion.

Although we have reported only two cases, we believe that they clearly show the need to study in much more detail the role of head, hands, and other parts of the body in the thermoregulation of infants under home conditions and the effects of different sleeping positions on temperature control and other physiological systems. Above all, they confirm the feasibility of detailed study of babies at home.

We thank the parents for allowing us to study their babies and intrude into their homes. We are grateful to Insight Visions for the loan of the camera, and the Foundation for the Study of Infant Deaths for funding the research health visitor.

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Continued need for pneumococcal prophylaxis after splenectomy

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Abstract

Two children died from pneumococcal infection five and eight years after splenectomy. Pneumococcal vaccination had not been given to either child. When the infection developed both children were not taking prophylactic penicillin. Vaccination and daily penicillin reduce the incidence of this complication and therefore we strongly recommend that both of these measures are continued indefinitely.

After splenectomy there is an increased incidence of bacterial infection of which *Streptococcus pneumoniae* accounts for 70% of the cases, most of the remainder being caused by other encapsulated organisms such as *Haemophilus influenzae* and *Neisseria meningitidis*.[1] Most infections occur within two years of splenectomy but the risk of infection is life long.[1]

Penicillin and pneumococcal vaccination may reduce the frequency of pneumococcal infection in such patients.[2 3] Such prophylactic measures are highlighted by two cases in whom prophylaxis was not given and who subsequently developed a fatal pneumococcal infection five and eight years after splenectomy.

Case reports

CASE 1

An 8 year old boy underwent splenectomy after abdominal trauma. Autotransplantation of splenic tissue was unsuccessful. He had not been vaccinated and had stopped taking prophylactic penicillin two years after splenectomy. Three years later, aged 13 years, he presented to his local hospital with a three day history of headache. A lumbar puncture was performed and *S pneumoniae* was isolated. Benzylpenicillin (60 mg/kg every two hours) and chloramphenicol (25 mg/kg every six hours) were commenced.

Twelve hours after presentation he developed signs of raised intracranial pressure. Mannitol 20% (1 g/kg) was given and he was transferred for further care. On arrival, a computed tomogram showed mild cerebral oedema with obliteration of the sulci. Six hours later he developed focal right sided seizures. He was therefore intubated and electively hyperventilated to maintain the arterial carbon dioxide tension between 3·0–3·5 kPa, and the total daily fluids were restricted to 30 ml/kg/24 hours. Twenty four hours later a repeat computed tomogram showed diffuse subarachnoid haemorrhage and extensive cerebral oedema. He died 10 days later.

CASE 2

A splenectomy was performed on a 4 year old boy for splenic rupture after abdominal trauma. No pneumococcal vaccine was given and prophylactic penicillin was stopped at 8 years of age.

When he was 12 years old he presented to his local hospital with septic shock after a 36 hour 'flu like' illness. He was cyanosed and hypotensive. Despite prompt resuscitation multiorgan failure developed within 12 hours of admission. He was then transferred to the regional paediatric intensive care unit. On examination the patient was moribund with gangrene of the extremities. Haematological investigations confirmed disseminated intravascular coagulation. *S pneumoniae* had been isolated in the blood and treatment with benzylpenicillin (50 mg/kg every four hours) and cefotaxime (75 mg/kg every eight hours) was continued. Despite aggressive management he died four hours after transfer.

Discussion

The incidence of overwhelming postsplenectomy infection or meningitis, due to *S pneumoniae,* varies in different series from 1·5% to 25%. The lowest incidence of infection after splenectomy (1·5%) occurs in children who undergo splenectomy because of trauma. When splenectomy is performed for an underlying haematological or oncological disorder—for example, Hodgkin's disease—the incidence can be appreciably higher (10%).[1] Because of the increased risk of such infection in children under 5 years of age and the 50% to 70% mortality associated with it,[1] physicians caring for such children need to be aware of the measures which may reduce its incidence. If overwhelming postsplenectomy infection does occur prompt resuscitation with the use of colloid to achieve haemodynamic stability as well as appropriate antibiotic and inotropic treatment may lessen the mortality.

Of the advice and measures available to reduce its incidence, the most important of all is to keep the parents fully informed of the predisposition of the child to overwhelming infection and this should be continually re-emphasised together with the need to seek urgent medical attention if the child becomes unwell.

A new pneumococcal vaccine Pneumovax II (Morson) and daily penicillin are the two most commonly available prophylactic measures. No definitive recommendation policy exists regarding their use, although recent proposals suggested that children at high risk, over the age of 2 years, should receive vaccination and be considered for revaccination every six years.[4 5]

Pneumovax II contains 25 μg of the capsular polysaccharide from each of the 23 serotypes that account for 90% of the pneumococci isolated from blood cultures.[4 5] Protection from pneumococcal infection after vaccination is thought to be depen-

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dent on achieving a good antipneumococcal antibody response and a serum antibody nitrogen concentration greater than 300 ng/ml is believed to offer protection for two to five years.[3] If possible vaccination should occur two weeks before splenectomy as higher antibody titres are produced. When a splenectomy is performed as an emergency such as after abdominal trauma, however, vaccination should still be performed because the antibody titres achieved are considered to be protective in most cases.

Although vaccination is generally thought to be effective, overwhelming pneumococcal sepsis in previously vaccinated patients does occur.[6] This may be due to several factors: (a) not all pneumococcal subtypes are covered in the vaccine; (b) the subtypes do not produce equal titres of antipneumococcal antibodies; and (c) the antibody titres, which may originally have been adequate, may decrease with time exposing the patient to pneumococcal infection.

Because of the latter reason revaccination of high risk adult patients has been performed with few side effects.[4] In children, however, revaccination is not currently recommended within six years of the primary vaccination.[4] Primary vaccination in children under 2 years of age is currently not recommended because of poor antibody production.

The Pneumovax II vaccine fails to cover all the pneumococcal subtypes. The loss of protection with time after vaccination because of the falling antipneumococcal antibody titres, repeated measurements of which in high risk patients would be logistically difficult to organise, means there is a need for a second concurrent prophylactic measure.

Prophylactic daily penicillin, which would theoretically cover all the pneumococcal subtypes, has been shown to be effective in reducing the incidence of pneumococcal sepsis in postsplenectomy patients. Its indefinite prophylactic use has been recommended in one study.[2] Poor compliance, allergic reactions, and the risk of producing penicillin resistant pneumococcal strains are the main problems cited with this approach.

Because of the previous reports on overwhelming postsplenectomy infection,[1 3] together with our own experience, we strongly recommend for all children who undergo splenectomy:

(1) Vaccination with Pneumovax II and revaccination at intervals of six years.

(2) Continuation of penicillin indefinitely or at least until the child has left an environment where there is an increased epidemiological risk of pneumococcal infection, such as school, university, or the armed forces.

(3) Continual parental awareness and vigilance.

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Visceral leishmaniasis in a Scottish child

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Abstract

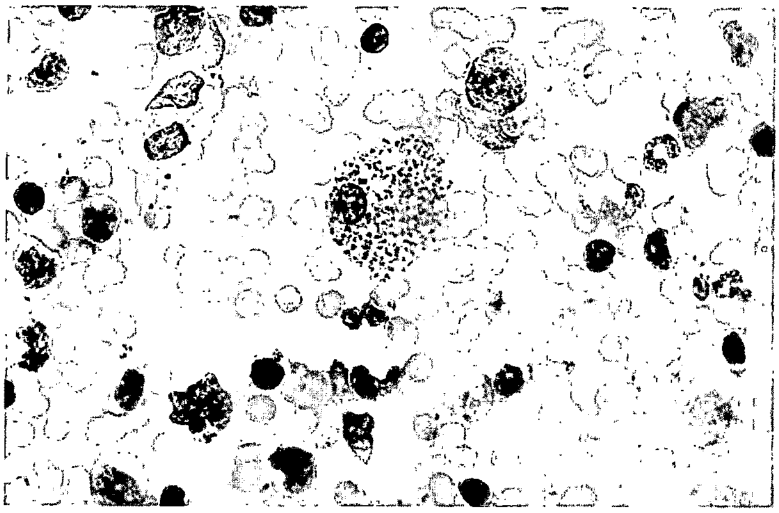
A Scottish girl acquired visceral leishmaniasis (kala-azar) while on holiday in Majorca. She presented with the infection, six months later, in Scotland. Because of inexperience with the disease and a degree of scepticism unnecessary investigations were carried out resulting in a delay in treatment.

Visceral leishmaniasis (kala-azar) is found in an area extending from the Straits of Gibraltar, across the Mediterranean through Asia to China. The vector is a sandfly, which transmits the infection from the natural reservoir usually an infected dog, to human beings during feeding. The sandfly does not survive in the colder climates north of the Mediterranean and leishmaniasis is virtually unknown in these countries.[1] Because of its long incubation period (six weeks to three years), however, it is possible for kala-azar acquired in an endemic area to present in a country where the disease is not endemic. We describe the case of a Scottish girl who acquired kala-azar while on holiday in a Mediterranean country and presented with the infection in Scotland.

Case report

A 9 month old girl was admitted to the Royal Hospital for Sick Children, Glasgow, with a 10 day history of lethargy, pallor, fever, and poor feeding. On examination she was found to have a mass in the left hypochondrium. She was febrile and miserable. Her haemoglobin concentration was 65 g/l, white cell count $6\cdot3\times10^9$/l, and platelets 41×10^9/l. Initially she was thought to be suffering from a malignant condition and was investigated accordingly. Bone marrow examination, blood culture, chest radiography, skeletal survey, and urine catecholamines were all normal. Abdominal ultrasound examination showed the mass to be a massively enlarged spleen.

She was given a blood transfusion and antibio-



Bone marrow showing presence of Leishman-Donovan bodies.

tics after which her general condition improved, although she continued to spike a fever two to three times a day. By the third day after admission, the results of the above investigations were all negative and the possibility of visceral leishmaniasis was raised. The child had been on holiday in Majorca six months earlier. The bone marrow was re-examined and again thought to be normal. Leishmania antibody titres were negative and as the condition was considered to be highly unlikely in a Scottish girl the diagnosis was discarded.

The girl remained febrile with increasing splenomegaly and hepatomegaly. Thrombocytopenia persisted and she also became neutropenic and was started on a neutropenic regimen.

Her fever did not respond to treatment with various antibiotics and repeated blood cultures were negative. Viral antibody titres to cytomegalovirus and parvovirus were negative as was her HIV antibody titre.

Three weeks after admission a bone marrow trephine was performed. A sample was sent to the London School of Hygiene and Tropical Medicine where the presence of Leishman-Donovan bodies was noted (Dr PL Chiodinie, consultant parasitologist). Re-examination of the original bone marrow also showed the presence of Leishman-Donovan bodies (figure).

The girl was treated with sodium stibogluconate 20 mg/kg/day for 10 days followed by 10 mg/kg/day for another 10 days. Her temperature settled within two days of starting treatment. Her platelet count returned to normal within seven days and by the 10th day of treatment her white cell count reached normal values.

She made an uneventful recovery and one year after completing treatment she remains perfectly well. Leishmania serology first became positive five weeks after presentation.

Discussion

We believe this to be the first case of kala-azar to be diagnosed in a child in Scotland. Because of inexperience with the disease and a degree of scepticism regarding the diagnosis, treatment of the condition was delayed by three weeks during which time the girl was subjected to a number of unnecessary investigations. In these days of global travel, with so many British tourists spending their holidays in the Mediterranean, it is likely that more cases of leishmaniasis will be seen in Britain because of the long incubation period.

The condition should be included in the differential diagnosis of any child or young adult, presenting with massive splenomegaly, severe anaemia, and thrombocytopenia who has been in an endemic area up to three years previously. Negative leishmania serology may not exclude the diagnosis during the initial stages of the disease as it may take a few weeks before becoming positive.

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Crohn's disease of the lung

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Abstract

Two years after developing colonic Crohn's disease, a 17 year old boy presented with focal pulmonary consolidation. A lung biopsy specimen showed areas of non-caseating epithelioid granuloma. Although some respiratory abnormalities appear to be associated with inflammatory bowel disease, granulomatous disease affecting the lung has not previously been reported in a child.

Crohn's disease appears to be a multisystem disorder,[1] but granulomatous pulmonary involvement has not been previously reported. We present our experience with a teenage boy.

Case report

A 15 year old boy was referred to hospital with a short history of diarrhoea, weight loss, and abdominal pain. Other features suggestive of inflammatory bowel disease included arthralgia, perianal inflammation, and erythema multiforme. At colonoscopy, a moderately severe pancolitis was found. Mucosal biopsy specimens were typical of Crohn's disease, showing non-caseating granuloma with epithelioid and histiocytic cells admixed with multinucleated giant cells (fig 1). The patient remained symptom free on maintenance treatment with mesalazine 400 mg three times a day, but two years later, developed left sided pleuritic chest pain, intermittent fever, and lassitude. A chest radiograph showed

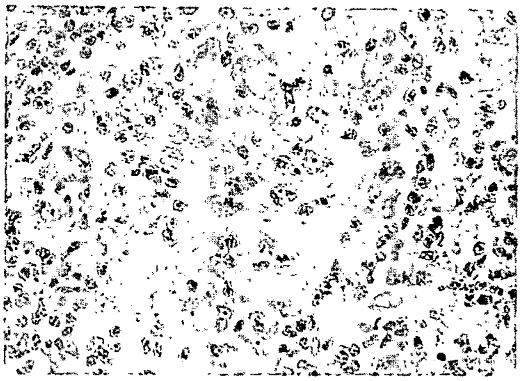

Figure 1 Colonic biopsy specimen showing a microgranuloma made up of epithelioid, histiocytic, and giant cells. (Haematoxylin and eosin ×192.)

patchy consolidation in the left lower lobe and when symptoms failed to respond to treatment with oral amoxycillin, admission to hospital was arranged for further investigations to be performed. He was noted to be pale and unwell with a persistent cough and fever. Radiological examination confirmed that the consolidation in the posterior segment of the left lower lobe was still present. In addition, there was a small pleural effusion which, like sputum, was sterile on culture. After treatment with erythromycin there was some improvement in symptoms, but several weeks later he became worse, with a productive cough and dyspnoea on moderate exercise.

INVESTIGATIONS

Investigations showed him to be anaemic (haemoglobin concentration 99 g/l) with a raised erythrocyte sedimentation rate (90 mm in the first hour) and plasma orosomucoids (2 g/l, normal <0·5 g/l). Repeated microbiological examinations of sputum, blood, gastric washings, and urine proved negative. Mantoux testing (1/1000) was also negative. A radioiostope lung scan indicated a matched ventilation/perfusion defect in the left lower lobe, and a thoracotomy with open lung biopsy was performed. The histological findings were of multiple focal areas of non-caseating epithelioid granuloma containing multinucleated giant cells in the interstitium, peribronchiolar, and perivascular regions (fig 2). Staining for micro-organisms including acid fast bacilli was negative as was tissue culture for mycobacteria; a Kveim test was subsequently negative.

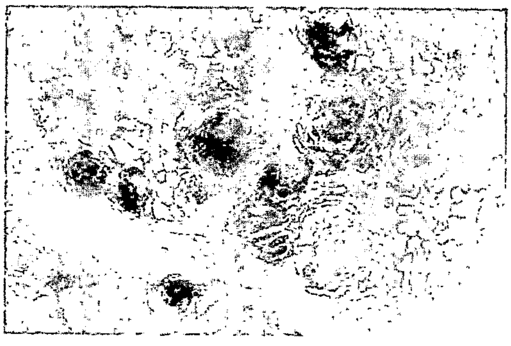

Figure 2 Lung biopsy specimen showing pulmonary parenchyma with multiple granuloma, similar to those in the bowel (see fig 1). (Haematoxylin and eosin ×78.)

CLINICAL PROGRESS

Treatment with isoniazid 300 mg and rifampicin 450 mg each day was started. Chemotherapy was discontinued three weeks later when all microbiological cultures proved negative. Steroids were not used. Fever and radiological abnormalities completely resolved over a further three weeks. In the next five years three relapses of Crohn's disease occurred with abdominal pain, weight loss, and diarrhoea, but without respiratory symptoms.

Discussion

Although Crohn's disease appears to be a multisystem disorder,[1] we know of no previous reports of granulomatous pulmonary involvement during childhood. Tuberculosis was initially considered the most likely diagnosis but was excluded by the absence of caseating granuloma, negative Mantoux tests, failure to identify mycobacteria histologically or on culture, and remission of symptoms after only a few weeks of antituberculous treatment. Sarcoidosis remains a possible alternative diagnosis, but is unlikely in view of the negative Kveim test. Chronic granulomatous disease was not investigated by tests of white cell function but would be very unusual in a boy who was well for the first 15 years of life.

Even though symptomatic pulmonary involvement in Crohn's disease may be rare, some studies have suggested that latent pulmonary involvement is a common finding.[2] Inflammatory bowel disease has also been linked with respiratory disorders such as chronic bronchitis (in the absence of smoking) and bronchiectasis.[3] Carbon monoxide transfer factor appears to be significantly reduced in patients with both Crohn's disease and ulcerative colitis when compared with control patients,[4] although some workers have disputed this finding.[5] It has been suggested that morphological and developmental similarities between bronchial and colonic epithelium may make both susceptible to damage from an unidentified humoral factor, or they might together be unduly sensitive to some external agent both inhaled and ingested.[6] The findings in our patient indicate that when Crohn's disease is complicated by granulomatous reactions in organs other than the bowel, the lung too may be involved.

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Topical anaesthesia for repair of minor lacerations

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Abstract

One hundred traumatic skin wounds were sutured under topical anaesthesia using a solution of lignocaine, adrenaline, and cocaine, and the effectiveness of the anaesthesia produced was assessed on a behavioural scale. The procedure was tolerated well by 63 patients, poorly by 11, and in 26 the response was uncertain. The response correlated well with age and with the field of anaesthesia measured from the wound margin. No toxic reactions were observed.

Minor lacerations resulting from falls, bumps, blows, or sharp objects are extremely common in young children. Often the most painful aspect of suture repair is the necessary infiltration of the wound margins with local anaesthesia, usually 1–2% solutions of lignocaine or amethocaine (tetracaine) hydrochloride. Suturing under topically applied solutions of amethocaine, adrenaline and cocaine has recently been described,[1–3] and this method appears to provide adequate local anaesthesia while being accepted by the patients at least as well as lignocaine infiltration. The degree to which topical anaesthesia is tolerated by children, however, remains unclear. This is principally due to poorly defined subjective methods that have been used previously to evaluate the child's response to the suturing procedure.[1–3]

Table 1 Scoring system for patients' before and during suturing

Score	*Behaviour*
1	Crying and requiring restraint
2	Crying not requiring restraint
3	Calm and flinching
4	Calm and motionless

Using a simple but objective method of pain assessment, this prospective study was undertaken to assess whether a topical solution of lignocaine, adrenaline, and cocaine (LAC) provides adequate anaesthesia for the suturing of skin lacerations in children under 13 years of age.

Patients and methods

Between September 1989 and February 1990, consecutive patients seen by two registrars (PJW and JM) at The Red Cross War Memorial Children's Hospital trauma unit with skin lacerations requiring suturing were included in the study. Patients with multiple or crush injuries, human bites, wounds more than 24 hours old, and those with a history of seizures, or any form of cardiac disease, were excluded. Mechanism of injury as well as site, type, and length of wound were documented. The topical anaesthetic solution was made up by the hospital pharmacy in 50 ml batches comprising 5·9 g cocaine (11·7%), 25 ml adrenaline (1:1000), 0·5 g lignocaine (1%), and normal saline to volume. The solution was stored at 15–20°C in a refrigerator specifically set aside for controlled drugs and has appeared to remain stable for up to three months.

A maximum volume of 3 ml (330 mg cocaine) was dripped into each wound over a period of 90 seconds after which the wound was loosely covered for 12–15 minutes with a sterile dressing. In children old enough to cooperate the field of anaesthesia from the wound edge was then measured to pinprick. Thereafter the wounds were prepared with 5% povidone-iodine solution and debrided as necessary. All wounds were primarily closed with simple, interrupted nylon sutures. The patients' behaviour, before as well as during suturing, was scored on a scale of 1–4 (table 1) by both the registrar and a disinterested non-medical observer from outside the trauma unit. All patients were asked to return to the unit for wound inspection and removal of sutures.

Results

During the study period 100 patients (69 boys and 31 girls) presented with lacerations which were sutured under topical LAC anaesthesia. The mean age was 5 years with only two patients under 12 months. Eighty five wounds resulted from blunt trauma, 13 from sharp objects, and there were two dogbites. Eighty four of the wounds were on the scalp or face. Only 11 wounds were visibly contaminated with dirt. Wound length ranged from 5–80 mm with a mean length of 15 mm. The field of anaesthesia could be assessed in 51 children and measured 3 mm or more in 43.

Out of a total of 100 registrar scores and 100 observer scores there was disagreement in only 12 instances of which eight were by one point only. As the discrepancy between the two sets of scores was so small, further analysis of results was performed using only the registrar's scores (table 2). The response of children who cried before and during suturing was considered to be uncertain. Partially because of unequal numbers in each category, there was no correlation between site, type, or length of wound and the children's behaviour. However, there was clearly an association between age, the field of anaes-

Table 2 Assessment of patients' behaviour according to doctors' score

Before suture	*During suture*	*Patient response*	*No of children*
1–2	1–2	Uncertain	26
1–2	3–4	Good	4
3–4	3–4	Good	59
3–4	1–2	Poor	11

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Table 3 Patient response by field of anaesthesia and age

	Patient response			*No of children*
	Good	*Uncertain*	*Poor*	
Field of anaesthesia (mm):				
Not measured	18	23	8	49
0–1	0	1	0	1
2	3	2	2	7
3	10	0	1	11
4	15	0	0	15
5+	17	0	0	17
Total	63	26	11	100
Age (years):				
<1	0	2	0	2
1–4	14	20	8	42
4–6	17	4	2	23
>6	32	0	1	33
Total	63	26	11	100

thesia measured, and the way in which suturing was tolerated (table 3). Forty nine out of 56 children over 4 years but only 14 out of 44 under 4 tolerated the procedure well. Also, a field of anaesthesia of 3 mm or more almost uniformly predicted a good response. Field of anaesthesia could be measured in five out of six children with lacerations of the lower limb and equalled 4 mm or more in all five.

Seventy two children returned to follow up and four wounds (6%) were clearly infected but had not dehisced. Pus swabs were taken from each wound and yield positive cultures for *Staphylococcus aureus* (n=2) and group A β haemolytic streptococcus (n=2). Each of these wounds were treated with suture removal and a topical antiseptic.

Discussion

Over the past two years we have sutured the vast majority of minor skin lacerations using topical LAC solution and have found overall that this regime is tolerated far better by children than when infiltration anaesthesia is used. Based on our experience we could not justify a comparison between topical LAC and lignocaine infiltration under trial conditions.

Long in use as the topical anaesthesia of choice for minor procedures on the nose, mouth, and pharynx, cocaine has recently been shown to be a safe and effective anaesthetic for use on the skin when combined with a vasoconstricting agent, usually adrenaline.[1] Cocaine is, however, a controlled substance and LAC solution is therefore more expensive than the equivalent amount of 1% lignocacine necessary for anaesthesia of minor lacerations and routine use in adults is probably not cost effective. In children, the advantages of producing local anaesthesia without using a needle hardly needs elaboration.

The technique of LAC application that we have used differs from those described previously. [3] Firstly, LAC was applied before the wound was prepared or irrigated so that minimal discomfort would be caused to the patient. Secondly, we slowly irrigated the wound with LAC to ensure maximal contact between the anaesthetic and the raw surface. Dressings, which could draw LAC out of the wound, were not applied. We believe that this technique ensured the best possible anaesthetic absorption at all sites including the lower limb. We are unable to explain the variation in fields of anaesthesia other than by psychic factors affecting the response to pinprick. The variation in the fields measured as well as the correlation between a wide field and a good patient response emphasises the importance of observing a standardised technique.

The evaluation of analgesic or anaesthetic medications in children remains a problem.[4] Because pain is an entirely subjective phenomenon it is virtually impossible to measure, particularly in an acutely injured child where the perception of pain is coloured by the acute trauma itself, past experience of pain or hospital visits, and parental attitudes.[5] In this study we used a simple observational measure of change in behaviour based on the premise that most children would cry or resist if they felt pain. The 94% agreement between the doctors' and observers' scores indicate that this method is acceptably valid for children of all ages and far less subjective than methods previously used in similar studies.[1–3] Twenty two of the 26 children who cried before and during the procedure were less than 4 years old and while no conclusions could be drawn in this group, the favourable results in the older children suggest that the distress observed in the younger age group might have been largely due to psychogenic factors.

The toxic effects of cocaine primarily involve the central nervous system ranging from mild excitability to convulsions and respiratory arrest in severe cases.[6] Toxic reactions have been described after application of cocaine to mucosal and burn surfaces[3] but not skin lacerations when a maximum dose of 350 mg cocaine per 3 ml solution used.[1 2] The addition of adrenaline provides local vasoconstriction allowing minimal systemic absorption of cocaine. Although this effect might theoretically interfere with wound healing, we observed no instances of wound dehiscence and the sepsis rate of 6% was similar to that reported previously with topical cocaine-adrenaline solutions.[1 2]

In conclusion, we believe that topical LAC provides good anaesthesia for the repair of minor lacerations in children and is therefore an acceptable alternative to traditional but painful infiltration anaesthesia.

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Commentary

Avoiding distress when treating lacerations in a trauma unit is a commendable objective and was achieved in this study in the majority of children over the age of 4 years. However, under 4 years of age, 68% of the patients were crying. Using adrenaline and cocaine 'dripped into the wound' avoided the pain of injecting lignocaine. Their previous unreported experience excluded the use of a comparison group of patients, so it is not possible to quantify any advantage of this technique. However, the authors do not caution against the use of adrenaline on extremities supplied by end arteries, but they justify the very high dose of cocaine by claiming minimal absorption with the 'local vasoconstriction' of adrenaline.

Before requesting the hospital pharmacy to supply this solution, paediatricians should consider the potential difficulties of storing two controlled drugs of uncertain stability unless kept at a defined temperature. Clear instructions must be issued excluding patients with a history of convulsions or cardiac disease and patients with lacerations on extremities or on mucosal or burnt surfaces.

This study suggests that the technique is not appropriate under the age of 4 years and provides no data to demonstrate that it is associated with less distress than cheaper and safer traditional infiltration with lignocaine.

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Lymphocytes bearing the T cell receptor $\gamma\delta$ in human breast milk

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Abstract

Lymphocytes bearing the T cell receptor $\gamma\delta$ (TCR–$\gamma\delta$) were searched for in human early milk lymphocyte suspensions by two colour cytofluorimetric analysis. It was found that the proportion of TCR–$\gamma\delta^+$ cells was twofold greater in colostrum than in either autologous or heterologous blood samples. Additional studies are needed to determine whether this particular subset of lymphocytes is involved in the lactation transmission of cellular immunity.

Although great strides have been made in defining the tissue distribution of, and receptor gene usage by, human lymphocytes bearing the T cell receptor $\gamma\delta$(TCR–$\gamma\delta$),[1] their migratory behaviour and homing mechanisms are completely unknown. Human colostrum and milk contain a substantial number of immunocompetent cells,[2] including T lymphocytes (CD3$^+$) of both helper-inducer (CD3$^+$/CD4$^+$) and suppressor-cytotoxic (CD3$^+$/CD8$^+$) phenotype.[3] In vitro, colostral T cells display certain characteristics of immunocompetence, but often possess antigenic reactivities different from those of the peripheral blood lymphocytes.[4] It has consequently been postulated that immune system cells are compartmentalised in the mammary gland during lactation and that T lymphocytes do not accumulate randomly in colostrum, but rather are directed there by a selective homing process.[4] With these findings in mind, we designed experiments to ascertain whether indeed TCR-$\gamma\delta^+$ cells do migrate to the mammary gland during pregnancy and lactation.

Materials and methods

Early milk samples were collected by manual expression from 15 lactating healthy mothers between days four and seven after delivery of normal term infants. The colostral lymphocytes were separated by equilibrium density gradient centrifugation as described by Richie *et al*.[3] Milk TCR–$\gamma\delta^+$ cells were phenotypically identified by an indirect immunofluorescence staining technique. The monoclonal antibodies used for staining were OKT3 (anti-CD3) (IgG$_{2a}$, Ortho) and anti-TCR δ 1 (IgG$_1$, T Cell Sciences) which binds to a δ constant region determinant of the $\gamma\delta$ heterodimer[1] and reacts with all known TCR–$\gamma\delta$ bearing cell clones and lines. Briefly, 1×10^5 cells were incubated for 30 minutes at 4°C with saturating concentrations of each antibody or with identical concentrations of isotype matched monoclonal antibodies that do not react with human cells. The cells were then washed twice and counterstained with goat antimouse F (ab')$_2$ subclass specific antisera conjugated with either fluorescein-isothiocyanate or phycoerythrin (Southern Biotechnology Associates). After two more washings, the monoclonal antibody bound to the cell preparations was assessed by flow cytometry (FACScan, Becton Dickinson). Data were collected from 20 000 cells per sample and analysed by a Hewlett Packard computer. Autologous and heterologous blood samples were similarly processed and the numbers of TCR–$\gamma\delta^+$ cells compared with those of the mammary secretions.

Results

As in previously published data,[3] the percent-

Lymphocytes bearing the T cell receptor $\gamma\delta$ *(TCR–*$\gamma\delta$*) in human early milk and peripheral blood*

Source of lymphocytes	*No samples tested*	*Mean % (range) CD3$^+$ cells*	*Mean % (range) TCR–$\gamma\delta^+$ cells**
Milk	15	68 (55–81)	11 (6–26)†
Postpartum blood	15	72 (60–84)	5 (0–18)
Normal blood	15	72 (60–86)	6 (1–15)

*CD3$^+$/TCRδ1$^+$ cells.
†$p<0·01$ (Wilcoxon's rank sum test) with respect to both postpartum and normal blood.

ages of milk and blood cells with a mature CD3$^+$ T cell surface phenotype were similar. Two colour cytofluorographic analysis, however, showed that the proportion of TCR–$\gamma\delta^+$ cells (CD3$^+$/TCR δ 1$^+$) was twofold greater in human early milk than in the peripheral blood (table).

Discussion

Although it is unlikely that colostrum TCR–$\gamma\delta^+$ lymphocytes are merely contaminating blood borne T cells, their origin remains enigmatic. Human TCR–$\gamma\delta^+$ cells populate organised lymphoid tissues (thymus, tonsil, lymph node, and spleen), as well as the gut and skin associated lymphoid systems, at similar frequencies without obvious tropism for epithelial microenvironments.[1] The recent demonstration in experimental animal models that enterally administered human milk leucocytes adhere to the gut epithelium or lie intramurally and persist in the intestine for at least 60 hours after a single breast feed, however, suggests that these cells may be involved in the host's local immune response.[5] The problem of whether TCR–$\gamma\delta^+$ cells play a part in the transfer of adoptive immunoprotection to the suckling infant remains unresolved. Now that some of the antigens these lymphocytes respond to have been defined,[6] however, the way is open to search for the answer. Finally, because of the specificity (δ protein) of the monoclonal antibody (TCR δ 1) used in this study, the possibility that breast milk contains lymphocytes which express just one of the TCR–$\gamma\delta$ chains cannot be totally ruled out.

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Intravenous immunoglobulin in virus associated haemophagocytic syndrome

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Abstract

A 1 year old boy with virus associated haemophagocytic syndrome caused by cytomegalovirus infection is described. Persistent severe thrombocytopenia responded to repeated intravenous infusions of immunoglobulin.

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Virus associated haemophagocytic syndrome is known to occur in association with herpes virus infections. Although the mortality is high, complete recovery has been reported. Immunoglobulin infusions have been shown to increase platelet counts in chronic immune thrombocytopenia. This treatment was effective in a child with severe persistent thrombocytopenia complicating virus associated haemophagocytic syndrome.

Case report

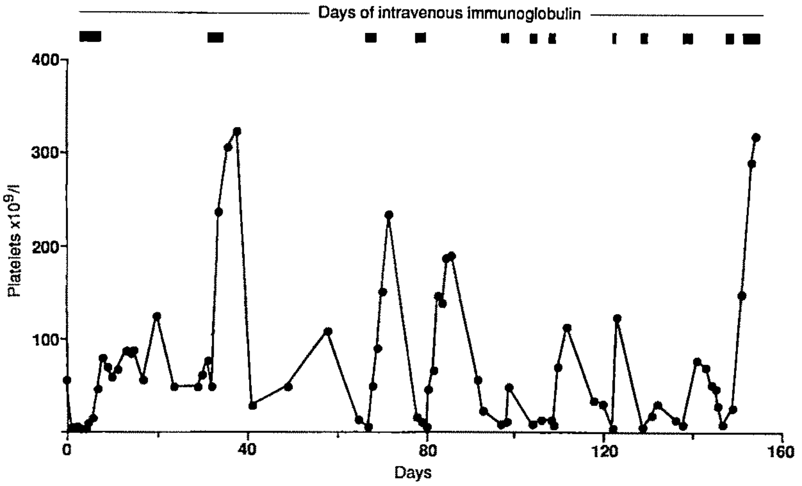
A boy aged 1 year presented with a one month history of intermittent fever and rash. Two days before presentation, he developed periorbital cellulitis, epistaxis, and a petechial rash.

He was the only child of healthy, unrelated parents. He had previously been well, had received no transfusions, and had been immunised with the full course of triple vaccine and oral polio. He was taking no medications.

On admission, he was febrile (39·1°C) with a diffuse petechial rash. There was generalised lymphadenopathy and appreciable hepatosplenomegaly. Examination of the nervous and respiratory systems was normal.

An initial peripheral blood count showed a haemoglobin concentration of 120 g/l, platelets 57×10^9/l, and a white cell count of $8·3\times10^9$/l, with an absolute neutrophil count of $0·08\times10^9$/l. Within 18 hours the haemoglobin was 83 g/l, the platelet count 4×10^9/l, and the total white count $2·7\times10^9$/l. Red cells were hypochromic and microcytic, and occasional reactive lymphocytes were visible. Clotting function was normal.

A bone marrow aspirate showed increased cellularity with active erythropoiesis, increased granulopoiesis, and plentiful megakaryocytes. Haemophagocytosis was present. There was no evidence of malignancy. A repeat bone marrow examination one month later was unchanged. An inguinal lymph node biopsy specimen showed reactive hyperplasia: the architecture



Changes in platelet count in relation to intravenous immunoglobulin treatment.

was preserved, prominent secondary follicles were present in an expanded paracortex, and there was some associated sinus histiocytosis. There was no evidence of associated haemophagocytosis nor any morphologic evidence of cytomegalovirus infection.

Virological investigations provided evidence of cytomegalovirus infection: cytomegalovirus IgM was present, cytomegalovirus was cultured from the urine on two occasions, and cytomegalovirus DNA hybridisation was strongly positive in buffy coat specimens. There was no evidence of infection with other herpes viruses, but an adenovirus type 2 was cultured from urine seven weeks after the initial presentation. An eye swab grew *Staphylococcus aureus*.

Tests of immune function showed no deficiency other than neutropenia. Serum immunoglobulin concentrations were normal. Total numbers of circulating lymphocytes, total T cells, and populations of CD4 and CD8 T cells were within the normal range. Increased numbers of activated B cells and natural killer cells were present, consistent with active viral infection. A direct Coombs' test was weakly positive.

Liver function tests were normal. Serum cholesterol and triglyceride concentrations were both within the normal range.

He was initially treated with intravenous antibiotics, platelet transfusions, and a transfusion of packed red cells. In view of persistent severe thrombocytopenia and bleeding manifestations, he was started on daily intravenous infusions of immunoglobulin at a dose of 0·4 g/kg/day for five days. A rise in platelet count was apparent on the fourth day of this course. Although the rise in platelet count was not sustained, the response to subsequent courses of immunoglobulin infusions was maintained (figure). This response was less noticeable with shorter courses of one or two days' immunoglobulin at the same dose.

His subsequent course has been uneventful, despite persistent severe neutrophils and recurrent thrombocytopenia associated with petechiae. A Hickman line was inserted to allow venous access. No measurable effect of the immunoglobulin infusions was apparent on haemoglobin concentration, total white cell count, or absolute neutrophil count. No side effects attributable to the immunoglobulin infusions were observed.

Discussion

The term 'virus associated haemophagocytic syndrome' (VAHS) was introduced to describe a disorder characterised by benign histiocytic hyperplasia and prominent haemophagocytosis associated with a systemic virus infection.[1] Herpes viruses, in particular cytomegalovirus, have been most commonly implicated, although since the original description the syndrome has been expanded to accommodate associations with non-viral infections and with other underlying illness including immune deficiency states, and has been termed 'haematophagic histiocytosis'.[2]

The clinical and histopathological features of this patient were consistent with the diagnosis of VAHS. Haemophagocytosis, histiocytic hyperplasia, and active cytomegalovirus infection were documented. There was no evidence of malignant proliferation of histiocytes, and serum lipids were not raised as may be found in other haemophagocytic syndromes, such as malignant histiocytosis and familial erythrocytic lymphohistiocytosis respectively.

There is no specific treatment for VAHS at present. Specific antimicrobial therapy has been used with success against bacteria associated with haemophagocytic syndrome and acyclovir in two patients with VAHS associated with Epstein-Barr virus.[3] There are no reports of the use of ganciclovir in the treatment of VAHS associated with cytomegalovirus.

Other approaches to treatment of VAHS have included immunosuppression. Both splenectomy and the use of steroids or vinca alkaloids have met with temporary success at best, however, and some authors have advocated reduction in immunosuppression as critical in the management of such patients. Etoposide has been successful in controlling haemophagocytosis in both familial erythrocytic lymphohistiocytosis and VAHS associated with Epstein-Barr virus, but did not affect the outcome in the latter patient.[4] Cyclosporin has been used in the long term treatment of haematophagic histiocytosis associated with Weber-Christian disease.[5]

There are no published reports of the use of intravenous immunoglobulin in this condition. A trial of this treatment was initiated in view of potentially life threatening severe thrombocytopenia.

The mechanism by which immunoglobulin caused an increase in platelet count in this patient is uncertain. The precise immunoregulatory disturbance that occurs in VAHS is uncertain, but the platelet count response to immunoglobulin suggests that the mechanism of platelet destruction has features in common with that in idiopathic thrombocytopenic purpura.[6] Low platelet counts precluded measurement of platelet associated immunoglobulin in this patient.

In conclusion, intermittent intravenous immunoglobulin has proved safe and effective in the treatment of severe persistent thrombocytopenia complicating VAHS.

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Do children need anticonvulsant treatment after a first fit?

The specious argument runs 'Epilepsy means recurrent fits. A single fit is therefore not epilepsy and does not require antiepileptic treatment'. The sensible argument depends on an assessment of the pros and cons of treatment. Estimates of recurrence risk after a first unprovoked seizure have varied from about 30% to 70%. A prospective study of 283 children in New York (Shinnat *et al, Pediatrics* 1990;85:1076–85) has given useful information. The overall risk of recurrence was 26% after one year, 36% after two years, 40% after three years, and 42% after four years. Factors increasing the risk were previous known cerebral pathology, abnormal electroencephalogram (EEG), and seizures of focal origin. Age at first seizure and duration of seizure did not influence the risk. Of 101 recurrences only two were status epilepticus and neither child suffered neurological sequelae.

The authors conclude that first unprovoked seizures should not lead to anticonvulsant treatment irrespective of risk factors.

The following table summarises the recurrence risks found in this study:

	% Recurrence risk (years)			
	1	*2*	*3*	*4*
Overall	26	36	40	42
Previous known brain pathology	37	53	60	
Idiopathic	24	33	36	
Idiopathic:				
Normal EEG	15	23	26	
Abnormal EEG	41	54	56	

ARCHIVIST

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REGULAR REVIEW

Helicobacter pylori

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Spiral organisms have been noted on the gastric mucosa on many occasions over the last 100 years. In 1975, Steer and Colin-Jones associated the presence of Gram negative bacteria on the gastric mucosa with gastritis.[1] However, their failure to culture the organism resulted in the finding being ignored. It was not until Warren and Marshall's report, in 1983, describing an association between the presence of spiral organisms on the gastric mucosa and antral gastritis in adults, that interest in a pathogenic role for bacteria in gastritis was rekindled.[2] Subsequent studies in adults and children have confirmed this association as well as a strong association with duodenal ulcer disease.[3 4]

This bacterium was initially referred to as a campylobacter like organism because of its morphologic resemblance to *Campylobacter jejuni*. After its successful culture, in 1984, the name '*Campylobacter pyloridis*' was applied to the organism but this was later changed, for grammatical reasons, to *Campylobacter pylori*. It has recently been designated as the type species of a new genus—termed 'Helicobacter'.[5] The organism, now called *Helicobacter pylori*, has been the dominant issue in recent studies on peptic ulcer disease.

H pylori is present on the gastric mucosa beneath the gastric mucus layer and within it.[3 6] The bacterium does not invade the epithelium. It is usually found on the antral mucosa but may also be present in other parts of the stomach. The organism colonises gastric tissue only.[7 8] *H pylori* may be isolated from other sites such as the duodenum, oesophagus, and rectum but only if there is gastric metaplasia at these sites.[8]

Antral biopsy specimens from colonised individuals show an increase in the number of mononuclear cells and in most cases there is an increased number of neutrophils present.[7] There is also depletion of intracellular mucin. Ultrastructural studies have demonstrated *H pylori* adhering to the surface of the gastric epithelium.[3] This adherence is associated with pedestal formation, a feature identical to that seen with enteropathogenic *Escherichia coli* attaching to intestinal cells.

Microbiological features of *H pylori*

H pylori is a spiral or curved, Gram negative, motile organism which has multiple unipolar flagellae. It produces large amounts of urease and is also catalase and oxidase positive.[3 5]

H pylori can be successfully cultured under conditions of reduced oxygen but does not grow under aerobic or anaerobic conditions.[5] Growth is optimal at 37°C. It has a long incubation period of five to seven days when grown in primary culture. *H pylori* can be grown on solid media such as charcoal, blood, or Skirrow's medium. A haemin source is always necessary for growth. Growth in liquid broth is possible when brucella broth is supplemented with fetal bovine serum.[5]

The bacterium is sensitive in vitro to penicillin, ampicillin, amoxycillin, erythromycin, gentamicin, kanamycin, rifampicin, metronidazole, tetracycline, and cephalothin. It is also sensitive to bismuth salts. Resistance to vancomycin, sulphonamides, trimethoprim, and nalidixic acid has been documented.[5]

To date no serotyping system has been developed. It appears possible to distinguish between strains using restriction endonuclease enzyme DNA digest pattern.[9] Using this method, isolates from each individual are almost always different, although the same strain can be isolated sequentially from an individual.

H pylori and gastritis

After Warren and Marshall's observation there have been many reports confirming an association between the presence of these organisms and gastritis in adults.[3 4] Almost all individuals with chronic antral gastritis are colonised. It was postulated that the organism could be colonising gastric tissue as a result of inflammation rather than as a cause of it. Subsequent studies in children demonstrated not only an association of *H pylori* with gastritis, however, but that the organism is associated specifically with primary or unexplained gastritis.[6 10]

Further evidence implicating *H pylori* as a gastric pathogen has come from volunteer studies. Two volunteers have ingested the organism and both developed gastritis after gastric colonisation.[11 12]

H pylori appears to have been associated with 'epidemic gastritis'. In 1979, Ramsey *et al* reported 17 healthy volunteers and one patient with Zollinger-Ellison syndrome who became profoundly hypochlorhydric while undergoing studies of acid secretion. These subjects simultaneously developed gastritis,[13] and it was subsequently possible to demonstrate rising titres of *H pylori* specific antibody after the onset of gastritis.[14] It should be noted that Morris became transiently achlorhydric when he ingested *H pylori*.[12] The reasons for this apparent achlorhydria at the time of acute infection with *H pylori* are not understood.

Newell *et al* have described the presence of *H pylori* in primates and found a similar association with gastritis in these animals.[15] A closely related organism, *Helicobacter mustelae*, has been identified on the gastric mucosa of ferrets.[5] This organism is also associated with gastritis. Ferrets are frequently found to have gastritis and peptic ulcer disease. Gnotobiotic piglets can be experimentally infected with *H pylori*. These piglets develop gastritis in association with gastric colonisation by *H pylori*.[16]

Perhaps the strongest evidence supporting a pathogenic role for *H pylori* in gastritis comes from treatment studies. These have demonstrated that eradication of *H pylori* from the stomach is associated with resolution of antral gastritis.[17-20]

H pylori and peptic ulceration

DUODENAL ULCER DISEASE

Duodenal ulcer disease is associated with chronic antral gastritis.[21] It is not surprising therefore that a strong association has now been demonstrated between the presence of *H pylori* on the gastric antrum and chronic duodenal ulcer disease.[3 4] The organism is present on the gastric mucosa in approximately 80% of adults with duodenal ulcers.[4] *H pylori* does not colonise the duodenal mucosa except at sites of gastric metaplasia.[7 8] This trophism for gastric tissue makes *H pylori* an unlikely candidate to cause directly duodenal ulceration. It has been proposed that gastric metaplasia in the duodenum serves as a precursor of duodenal ulceration by providing a nidus for *H pylori* colonisation and subsequent inflammation.[8]

Although the role of *H pylori* in duodenal ulceration is not understood, its importance in this condition is demonstrated by the effect of clearing this organism on duodenal ulcer disease. Relapse rates for duodenal ulcer disease are appreciably reduced when *H pylori* is cleared from the gastric mucosa.[17]

GASTRIC ULCER DISEASE

The association of *H pylori* and antral gastritis with gastric ulcer disease is less noticeable. The organism is found in approximately 60% of adults with gastric ulceration.[4] This may be due to the fact that a significant number of gastric ulcers are secondary, being related to drug and other ingestions.

H pylori in children

Several studies have confirmed an association between gastric colonisation with *H pylori* and antral gastritis in children.[6 10 22-26] There also appears to be a strong association between *H pylori* associated antral gastritis and chronic duodenal ulcer disease in children.[6 22 26]

In 1987, a prospective study in Toronto, examined antral biopsy specimens from 67 of 71 children who underwent upper gastrointestinal endoscopy.[6] Forty nine of these children had normal antral histology and 18 had histological gastritis. Of these 18, 10 had unexplained gastric inflammation whereas eight had an underlying cause identified (gastroduodenal Crohn's disease, eosinophilic gastroenteritis, drug ingestion). Seven of the 10 children with primary or unexplained gastritis had *H pylori* isolated from the gastric mucosa. In contrast none of the children with secondary gastritis had *H pylori* isolated. Also none of the 49 children with normal histology had the bacterium cultured from biopsies. A retrospective study using gastric biopsy specimens, obtained over a three year period, resulted in identical findings.[10] These studies provided strong evidence implicating *H pylori* as a gastric pathogen.

The number of children colonised with *H pylori* is very low, in Western societies, in comparison with the number of adults colonised.[22 27] Colonisation increases progressively with age.[27] The prospective study in Toronto found *H pylori* gastritis in only 10% of children undergoing endoscopy for upper gastrointestinal symptoms.[6] Hill *et al* found the organism in six of 38 (16%) children studied in Australia.[23] Cadranel *et al* found *H pylori* in eight of 25 children (32%) studied in Belgium.[24] More recently Glassman *et al* detected the organism in 10% of children undergoing upper endoscopy in New York.[25] Studies of children, in Western societies, indicate that colonisation almost never occurs below 8 years of age.[6 10 22 23 25]

PEPTIC ULCER DISEASE

In two prospective studies from Toronto *H pylori* was found in association with duodenal ulcer disease in all 13 cases in which ulcers were detected.[6 22] In a retrospective study Kilbridge *et al* found *H pylori* to be present on the antral mucosa in eight of nine patients who had duodenal ulcer disease.[26] Therefore, although duodenal ulcer disease is uncommon in children, there is a strong correlation between the presence of such ulceration and *H pylori* associated antral gastritis. An association with gastric ulcer disease has not been clearly demonstrated as primary gastric ulceration is rare in children.[28]

SYMPTOMS

There has been no major prospective study of presenting symptoms in children colonised with *H pylori*. Epigastric pain and vomiting appear to be major presenting symptoms.[6 24 25] Children with duodenal ulcer disease have more noticeable symptoms than those with gastritis alone.[19]

Clearing of *H pylori* from the gastric mucosa and resultant improvement or healing of gastritis is associated with a definite improvement in symptoms. This improvement in symptoms is, however, primarily seen in those patients who have associated duodenal ulcer disease.[19] Oderda *et al* found that clearing *H pylori* from the gastric mucosa using amoxycillin alone resulted in the disappearance of symptoms in children.[29] Although the infection recurred in most of the children, however, very few developed a relapse of symptoms. Therefore, *H pylori* associated gastritis, in the absence of ulcer disease, may not be a significant cause of symptoms. This supposition is supported by the finding that *H pylori* colonisation is widespread in the adult community as well as in siblings of children with documented *H pylori* gastritis.[22 27] Large prospective studies of children undergoing endoscopy will be needed to clarify this issue.

ENDOSCOPIC FINDINGS

Children and adults with *H pylori* associated gastritis often have normal endoscopic findings.[6 18] It is essential to obtain antral biopsy specimens during endoscopy. These specimens may demonstrate appreciable gastritis microscopically in the absence of endoscopic findings.

Diagnosis of *H pylori* infection

CULTURE

The 'gold standard' for diagnosis of *H pylori* infection is culture of the organism from an antral biopsy specimen. The specimen can be ground and the material used to inoculate blood agar, chocolate agar, or Skirrow's medium.[5 6] These inoculations should be done within 60 minutes of the biopsy being taken. The plates are incubated at 37°C under microaerophilic conditions for up to seven days. *H pylori* colonies are very small and translucent and usually very few colonies are present on a primary culture from a child. The organism is identified as *H pylori* if it is positive for urease, catalase, and oxidase and produces a negative reaction for hippurate hydrolysis and nitrate reduction.[5]

STAINING TECHNIQUES

Because of its spiral appearance and unique location within and beneath the gastric mucus layer, *H pylori* can be demonstrated by various stains on histological sections. The Warthin-Starry silver stain has been widely used to demonstrate the organism. The silver stain allows for easy identification of darkly staining bacteria against a bright background. This method of identifying *H pylori* correlates very well with culture in children.[6 22] However, these stains are tedious to perform. Simpler methods include the use of a giemsa stain which is also very effective.[7 29]

UREASE TESTS

A positive urease reaction occurring when a gastric biopsy specimen is incubated in a urea medium is usually indicative of the presence of *H pylori* on the gastric mucosa. The biopsy specimen is placed on a Christensen's urea slope and a positive reaction is indicated by a change in colour of the medium from tan to pink.[30] Commercial tests for urease production can identify *H pylori* in approximately 90% of biopsies from colonised children.[29]

Urease breath tests have been developed to detect *H pylori* colonisation by non-invasive means. Labelled urea (^{13}C or ^{14}C) is ingested by individuals and the breakdown of urea by bacterial urease results in the appearance of labelled carbon dioxide in the expired air of colonised subjects.[31 32] Quantitation of expired labelled carbon dioxide allows for the indirect diagnosis of *H pylori* gastritis. These tests are extremely sensitive. A ^{13}C label is more ideal for use in children as it is not radioactive. The label, however, is very expensive and the test requires the use of mass spectrometry.

SEROLOGY

A *H pylori* specific IgG serologic response is both highly sensitive (96%) and highly specific (99%) in identifying children with *H pylori* associated gastritis.[22] Enzyme linked immunoabsorbent assay systems are now widely used to detect this serological response using various *H pylori* antigenic preparations. The IgG immune response is the most sensitive indicator of infection. The IgA immune response is also used whereas specific IgM measurements are not reliable.[27] Serological testing may therefore, present a very good diagnostic test for *H pylori* associated gastritis in children.

Epidemiology

Serology has provided the optimal means of studying the incidence of *H pylori* colonisation. In Western countries, studies have shown that children and young adults are rarely colonised by *H pylori*.[22 27] The incidence of infection increases progressively with age until approximately 50–60% of the population are colonised at 60 years.[27] The reason for this increase in colonisation with age is not known. There are indications that colonisation occurs earlier in life and ultimately effects almost the entire population in less developed countries.[33]

H pylori has not been isolated from a site outside of the gastrointestinal tract. There is a single report of successful culture of the organism from dental plaque.[34] There is no known natural reservoir in the environment for this bacterium. A recent study of children and their families provides strong evidence supporting person to person transmission of this organism.[22] In this study, 73% of parents of *H pylori* positive children had a *H pylori* specific serological response, whereas only 24% of parents of children who were not colonised had such a response. The strongest evidence of person to person spread was provided by studies on the siblings of the *H pylori* colonised children. Eighty one percent of these siblings were found to have serological evidence of *H pylori* colonisation in comparison with 13% of controls.

It is unclear whether members of a family are colonised by the same strain of *H pylori*. Strain identification using DNA digest patterns has shown the same strain infecting several members of the same family in Europe. In Canada, however, young siblings were shown to be colonised by different strains.[9] Furthermore, it appears that an individual can harbour more than one strain of the organism simultaneously.[35] Further studies are therefore needed to clarify this issue.

Treatment

Eradication of *H pylori* from the gastric mucosa is correlated with healing of antral gastritis in adults and children.[17–20 36] This occurs irrespective of the particular agent that is used to clear the organism. While *H pylori* is sensitive to many antibiotics in vitro, this sensitivity is not correlated with clearing of the organism in vivo.[37] It has been postulated that the failure of antibiotic monotherapy adequately to clear *H pylori* in vivo may be due to the lack of efficacy of the antibiotics in the acid environment of the stomach.[37]

H pylori is optimally cleared from the gastric mucosa using combinations of bismuth salts and various antibiotics.[20 37] Treatment with bismuth salts alone is successful in clearing *H pylori* from the gastric mucosa in approximately 50% of adult patients.[17 18 20] Recurrence of infection is common after treatment of *H pylori* by bismuth alone or antibiotic monotherapy.[20 29]

Oderda *et al* treated children with amoxycillin. Immediately after treatment the organism was absent from gastric biopsy specimens in 85% of treated children.[29] However, three months later the infection was present in 73% of these children. Combination therapy using a bismuth preparation and an antibiotic such as ampicillin or metronidazole increases the percentage of adult patients in whom the organism is cleared.[20 37] Studies from Leeds and Toronto have reported clearing of *H pylori* from the antral mucosa in 70% of children treated with bismuth subsalicylate or tripotassium dicitrato bismuthate and oral ampicillin (MJ Mahony, JI Wyatt, JM Littlewood; British Society of Gastroenterology, Autumn 1989).[19] In Italy, 94% of children treated with amoxycillin and tinidazole were successfully cleared of *H pylori* and six months later 75% of them remained clear.[36] There are, however, ethical considerations in performing repeat endoscopies on asymptomatic children and long term relapse rates will be difficult to determine. More recently triple therapy using bismuth combined with two antibiotics, such as amoxycillin and metronidazole, has been reported to be successful in long term eradication of *H pylori*. Evidence is accumulating that *H pylori* rapidly develops resistance to antibiotics such as metronidazole, however, although resistance is less likely to occur when the antibiotic treatment is combined with bismuth. Such triple therapy is not presently justified in situations other than controlled trials.

DUODENAL ULCER DISEASE

H_2 antagonists have appreciably reduced the morbidity associated with chronic peptic ulcer disease. However, relapse of ulcer disease occurs in most patients (children and adults) after treatment is stopped.[17 28] These agents have no effect on *H pylori* colonisation or on the chronic gastritis that is invariably associated with duodenal ulcer disease.[18 20] Bismuth salts are as successful as H_2 antagonists in healing duodenal ulcers. More importantly, duodenal ulcer disease relapses less frequently after treated with bismuth.[38] This appears to be due to the effect of bismuth on *H pylori* associated antral gastritis.[17] Recent studies have shown a considerable reduction in the rate of relapse of duodenal ulcer disease if *H pylori* is cleared from the gastric mucosa during treatment.[17] Recurrence of ulcer disease in such patients is associated with reinfection with *H pylori*.

RECOMMENDATION ON TREATMENT

While the search is continuing for the optimal treatment of *H pylori* associated gastritis, we have to define who requires treatment. There is, at present, no evidence to indicate that treatment is necessary for *H pylori* associated gastritis in the abscence of ulcer disease. Chronic duodenal ulcer disease in children has a natural history identical to duodenal ulcer disease in adults.[28] The evidence from studies in adults would seem to justify treating children with duodenal ulcer disease using colloidal bismuth subcitrate (bismuth chelate, tripotassium dicitrato bismuthate) for four weeks combined with an antibiotic such as ampicillin or metronidazole for two weeks. Mahony *et al* used colloidal bismuth subcitrate, 240 mg twice a day in children and did not encounter bismuth toxicity (MJ Mahony, JI Wyatt, JM Littlewood; British Society of Gastroenterology, Autumn 1989).

Conclusion

H pylori is a cause of chronic antral gastritis. Furthermore, clearing of *H pylori* from the gastric mucosa reduces the rate of relapse of duodenal ulcer disease. Several questions still need to be studied if we are to fully understand the role of this bacterium in peptic disease. There have been hypotheses published to explain how *H pylori* colonisation could result in chronic duodenal ulcer disease. These hypotheses have relied on the ability of *H pylori* to break down mucus. A recent study indicates that *H pylori* is not effective in degrading mucus.[39] This association between antral gastritis, *H pylori*, and duodenal ulceration is therefore still not understood. Why does the organism colonise gastric tissue only? How does *H pylori* cause inflammation? Is there a natural reservoir for this organism in the environment? Research projects are presently being undertaken in several centres that will hopefully provide answers to these questions.

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CURRENT TOPIC

The cytokines are coming

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On 31 March 1980 the front cover of *Time* magazine was devoted to 'Interferon—The IF drug for cancer'. Whatever happended to interferon, which seemed to promise so much, and why did it not live up to early expectations? The answer may lie with Dr K Cantell, a pioneer worker with interferon, when he stated that: 'Much second class research was carried out with third class preparations slightly contaminated with interferon'.[1] Such studies were necessarily performed with the tiny amounts of interferon obtained from vast pools of donated blood. The revolution in genetic engineering over the past decade has enabled large quantities of pure interferon and other cytokines to be produced. So 10 years after a false start we are ready to try again: the cytokines are coming.

What are they?

From the evidence of in vitro studies alone, these extremely potent polypeptides seemed to fall into two broad functional groups. Those with a primary regulatory action on mature cells were called cytokines, with the additional distinction that lymphokines were made by lymphocytes (for example, interleukin 2, IL-2) and monokines by monocytes (for example, interleukin 1, IL-1). The others, characterised by their ability to support the proliferation and differentiation of immature precursor cells were labelled growth factors (for example, fibroblast growth factor α) or, more particularly in the haemopoietic system, colony stimulating factors (for example, granulocyte macrophage colony stimulating factor). This distinction has blurred as cytokines have been found to have growth factor activity and vice versa (for example, interleukin 3 was found to be the same molecule as multi-colony stimulating factor). While the terminology is in a state of flux, 'cytokine' remains arguably the most appropriate generic term.

More than 30 peptides are currently recognised as cytokines, having been purified, sequenced, and the coding genes cloned. Together they form a network divided into five broad groups:

- Interferons (IFN-α, β and γ)
  Originally recognised by their ability to protect cells from viral infection.
- Interleukins (IL-1 to 9)
  Diverse immunoregulatory factors named in historical sequence.
- Haemopoietic colony stimulating factors (erythropoietin, granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF)
  Structurally dissimilar, but functionally related in controlling haemopoiesis.
- Tumour necrosis factors (TNF-α and β)
  Structurally related proteins with cytotoxic activity in vitro.
- Assorted growth factors (for example, platelet derived growth factor)
  Named according to the cell system in which their activity was discovered.

As our understanding increases, the composition of these basic groups will undoubtedly change. The haemopoietic colony stimulating factors constitute a functionally related group, which is reflected in their orderly nomenclature. Though new members of the group may appear, the names of the existing factors are unlikely to alter. In contrast, interleukins are a heterogeneous group, simplistically numbered as they were discovered, with the consequence that future changes of name are inevitable (for example, IL-6 is the same protein as interferon IFN-β_2).

What do they do?

Cytokines control both specific and non-specific aspects of normal growth, inflammatory repairs, and immune responses throughout the body. The necessary level of integrated control is achieved through a network of cytokines and receptors that can interact rapidly within a locally contained environment.

Each cytokine acts through its own specific receptor situated on the surface of the target cell. A receptor that has been bound by cytokine transduces a signal into the interior of the cell. After further cytoplasmic interactions this signal results in altered gene transcription, protein synthesis, and changes in the metabolic state of the cell. The level of high affinity receptor expression does not remain constant on any given cell, varying with the state of cellular activation. Depending on this state, binding of a cytokine may increase or decrease the subsequent expression of its receptor on the target cell, leading to up or down regulation, respectively, of responsiveness to further cytokine exposure. Additionally, cytokines are able to cross regulate the expression and affinity of each other's receptors and thereby ensure a well coordinated response.

Whereas endocrine hormones have their sites of action away from where they are secreted, cytokines tend to act locally as either paracrine (that is, within a small cluster of cells) or autocrine (that is, autoregulating the cell producing the cytokine) factors. The reason for this lies in the requirement for networks like the immune system to produce separate responses to numerous local challenges at any given moment, only resorting to total commitment of resources in the face of a potentially overwhelming attack. To some extent this organisational structure underlies many of the problems encountered with systemic cytokine treatment. Attempting to treat malignancy by flooding a patient's systemic circulation with an immunoregulatory cytokine is rather like defibrillating a malfunctioning computer. One is mechanistically none the wiser—even when successful. On the other hand, some cytokines also seem to have a more generalised action. For example, evidence is accumulating that in addition to its local action in inducing B lymphocyte differentiation, IL-6 may be an important systemic inducer of acute phase proteins.[2]

Given their pivotal role in the regulation of cell growth, it is not surprising that cytokines and their receptors have oncogenic potential. The viral oncogene carried by the simian sarcoma virus (v-*sis*) induces malignant transformation of fibroblasts in culture. Sequencing shows that the v-*sis* oncogene incorporates the entire code for the β chain of platelet derived growth factor.[3] A cell infected with this virus therefore becomes committed to producing unchecked amounts of a potent growth factor. On the other side of the cytokine/receptor interaction, the feline sarcoma virus carries the v-*fms* oncogene, which codes for an aberrant form of the receptor for M-CSF. After infection by the virus the cell manufactures the abnormal receptor, which is then inserted into the plasma membrane. Here it acts as a permanently activated receptor, falsely informing the cell that it is constantly exposed to M-CSF. The end results are unregulated proliferation and in vitro malignant transformation.[4]

Current clinical applications

Trials of cytokines have proliferated with the increased availability of industrially manufactured 'recombinant' proteins. On the basis of their currently understood in vitro actions, cytokines are being used as supportive, cytotoxic, or immunomodulatory factors.

SUPPORTIVE FACTORS

The haemopoietic colony stimulating factors lend themselves to clinical use for several reasons. As a consequence of the availability of good in vitro models, their role in regulating haemopoiesis is comparatively well understood. Their actions are fairly specific and they are relatively non-toxic in vivo. Lastly, their efficacy is reasonably easy to monitor.

Trials of GM-CSF in the treatment of aplastic anaemia have produced some promising early results. Initial improvements in numbers of circulating monocytes and granulocytes have been reported in moderately severe cases, but so far responses have not been sustainable.[5] This is not altogether surprising as the primary action of GM-CSF is in the later stages of haemopoiesis, whereas the defect in aplastic anaemia is usually at the stem cell level. Perhaps cytokines that do influence pluripotential stem cells will produce better responses in future trials.

Both GM-CSF and G-CSF have been used in the treatment of primary neutropenias with varying success. A recent German trial has shown that while both are clinically beneficial in children with severe congenital neutropenia, G-CSF has more potential for producing sustained neutrophil responses with associated improvements in defence against bacterial infections.[6]

Neutropenia remains the single most important limiting factor in many cancer chemotherapy and transplant regimens. Consequently, the ability of haemopoietic colony stimulating factors to accelerate bone marrow reconstitution is under intensive investigation and plans for the first United Kingdom Children's Cancer Study Group trial of GM-CSF are well advanced. If myelotoxicity can be adequately countered with colony stimulating factors patients will be less vulnerable to opportunistic bacterial infections and may be able to tolerate more intensive chemotherapy. As the results from many centres accumulate, a clear international consensus is emerging that both G-CSF and GM-CSF are beneficial in treating neutropenic adults and are likely to be incorporated into routine chemotherapy regimens.[5] The potential role of colony stimulating factors in the treatment of thrombocytopenia remains to be explored.

Supportive cytokine treatment is of potential benefit in other groups of compromised patients. Giving GM-CSF to leukopenic AIDS patients has been shown to produce dose dependent increases in circulating white cells.[7] In paediatric practice treatment with erythropoietin is under investigation as an alternative to blood transfusion in anaemic premature babies[8] and children with renal failure.[9] Consideration is also being given to the use of cytokines to enhance neutrophil function during episodes of neonatal infection.[10]

CYTOTOXIC FACTORS

IFN-α, IFN-β, and TNF-α each have a direct antiproliferative influence on tumour cell growth in vitro. Clinical trials of IFN-α have shown antitumour activity in patients with chronic leukaemia, lymphoma, carcinoid, glioma, Kaposi's sarcoma, melanoma, and a variety of carcinomas. Response rates vary from 90% in hairy cell leukaemia to 11% in melanoma.[11]

In contrast, results obtained using TNF-α as a single agent have been disappointing. Its potential for toxicity, as one of the physiological mediators of septic shock, has proved a serious limiting factor in clinical trials. Tumour regression has been shown in a minority of patients and, consequently, TNF-α may still have a role when used in combination with other cytokines.[12] It remains to be seen whether these anticancer effects are the result of direct cytotoxicity or of as yet unrecognised in vivo immunomodulation.

IMMUNOMODULATORY FACTORS

Two cytokines, IL-2 and IFN-γ act through their ability to augment the host's normal immune responses.

During incubation with IL-2, lymphocytes develop greatly increased cytotoxic potential—so called lymphokine activated killing (LAK)—and will kill virtually any cancer cells that they make surface contact with in laboratory assay systems. Initial clinical trials, in which patient's lymphocytes were harvested, activated in vitro with IL-2 and then reinfused, were carried out at the United States National Cancer Institute. Promising response rates were obtained in 38% of patients with a variety of metastatic tumours that were resistant to conventional treatment.[13] Unfortunately the high dose regimens used were severely toxic and many patients required admission to the intensive care unit. The biological responses produced in these trials were so impressive (featured on the cover of *Time* magazine in the mid 80s) that numerous groups throughout the world have designed clinical trials that attempted to dissect out the beneficial from the toxic effects of IL-2/LAK treatment. Interestingly, recent reports have suggested that in vivo reinfused LAK cells do not actually go near to the tumours that they destroy.[14] Thus the initial laboratory phenomenon of LAK activity, which requires lymphocyte—tumour cell contact, is probably unrelated to the antitumour effects of LAK treatment.

IFN-γ has widespread effects throughout the immune system, including activation of macrophages, T cells, B cells, and natural killer cells and induction of class II major histocompatability complex molecules.[15] As well as its potential for antitumour immunomodulation, it is an important factor in host defences against microbial attack. Together with the other interferons there are encouraging preliminary reports in various infectious diseases including IFN-α in chronic hepatitis B infection[16] and IFN-γ in leprosy.[17]

Cytokine biology is proving to be of interest to other disciplines in which immunoregulation may be therapeutically beneficial. In particular, as a result of the increased appreciation of the inter-relationship of autoimmunity and the cytokine network, there is burgeoning interest among rheumatologists.[18]

The future

Numerous candidate proteins are queuing for official admission to the cytokine network. As molecular biological techniques continue to advance the speed with which new factors can be cloned will increase. Each cytokine comes with an individual receptor and, in addition, many seem to have an almost structurally identical but antagonistic 'anti-cytokine'.[19] Consequently, the number of accepted cytokines and associated molecules will grow rapidly during this decade.

As cytokines emerge from the laboratory and move into the clinic, false starts, disappointments, and unexpected problems are to be anticipated. To minimise these set backs it is essential that we direct our efforts to understanding how cytokines function under normal and pathological conditions in vivo. As our fundamental understanding of the cytokine network increases, so does the potential to modify it with recombinant cytokines or with drugs—as we have almost certainly been doing for years without realising it.

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Archives of Disease in Childhood 1990; 65: 1286–1287

PERSONAL PRACTICE

Head injury—how community paediatricians can help

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Every year in this country 45 of every 1000 children under the age of 14 years are admitted to hospital with closed head injuries; these account for 5% of all paediatric admissions.[1] Most of them have 'minor' head injuries and are discharged within 48 hours, but a small number (about 5%) have severe head injuries.[2] Of these, half will be left with residual motor or cognitive impairment.[3–6] Without early and appropriate rehabilitation many will rapidly develop secondary damage.

A recent report of the Paediatric Neurology Association draws attention to the lack of consistency in the way such children are managed, and recommends that follow up should offer paediatric neurological and neurosurgical expertise.[7] In practice, those who are admitted to neurosurgical units (and most are not) are returned to their local paediatric wards as soon as they cease to need surgical intervention or intensive care. Management of the early rehabilitation and follow up are usually, therefore, the responsibility of the general paediatrician. It is disturbing that such an important cause of childhood morbidity is not yet being tackled systematically throughout the country, but in the meantime what can paediatricians do to help these children?

Developmental rehabilitation as a specialty

Most paediatricians do not have the specialist knowledge required to build up and lead a multidisciplinary, multiagency team for the assessment and rehabilitation of the small but constant numbers of children with head injuries who come under their care. The basis for such a service already exists in many districts, however, in the form of the child development team (formerly the district handicap team), and expertise in the specialised field of acquired brain injury comes naturally to community paediatricians with neurodevelopmental training. It seems logical therefore to consult them from the outset so that there is a continuum of rehabilitation through hospital admission to reintegration into the local community.

Such a scheme of developmental rehabilitation need not be confined to head injuries. There are many causes of acquired developmental damage—chronic illness, major or repeated operations—which would benefit from this.

What should such a service provide?

IN THE EARLY STAGE OF REHABILITATION OF SEVERE HEAD INJURY

(1) Assessment of premorbid development from community health and educational records.

(2) Thorough neurological examination to detect even the most minor residual structural damage, including defects of vision or hearing.

(3) Coordination of a planned assessment programme to include:

● Detailed psychometric testing of cognitive, visuospatial, and memory function.

● Assessment of speech and language.

● Observation in an educational setting to assess distractibility, retention of preaccident learning, and the processing of new information. It may be inappropriate to make an official 'Statement of special educational needs' while the child is still improving, but suitable temporary educational provision must be made for children of school age as soon as they are well enough to attend school even part time. Such provision may initially be in the hospital school, particularly if an intensive programme of physical rehabilitation is necessary. It is essential to know what facilities are available locally and in specialist units, to be able to liaise with both the hospital school and the child's original school, and to advise the parents and educational authorities accordingly.

● Housing, mobility, and self help skills must also be assessed. Early notification of changed housing needs and appropriate use of occupational therapy services to advise and organise aids and seating ensures that a child is not kept in hospital beyond the optimal length of inpatient rehabilitation.

(4) Supervision of a multidisciplinary plan of rehabilitation.

(5) Counselling, support, and information. Parents, and sometimes children, understandably feel optimistic during the phase of rapid recovery. They tend to concentrate on physical recovery and do not appreciate that learning problems are likely to prove the most disabling long term outcome. Their grief reaction may be delayed until the reality of permanent impairment becomes established. Long term psychological support from a professional person with a knowledge of the possible after effects of head injuries is therefore essential. This can often be

provided by the paediatrician or psychologist, or both, who may also be needed to help with the behavioural results of head injuries, and to modify the family response to the child. Litigation features prominently in many cases, and as after other types of accident, it is essential to keep the parents informed of the details of the child's condition and the possible long term outcome, to concern them in management plans, and to put them in touch with helping agencies.

WHEN CHILDREN PRESENT AT A LATER STAGE

From time to time children are referred with developmental, behavioural, or learning problems who have apparently fully recovered from a previous head injury. As one in 15 children has had a head injury 'which caused parents serious worry' there are many who present in this way.[8] It is important to attempt to establish the relative importance of the injury to the current problems, and this can only be achieved by detailed assessment of the child and his or her home and educational environment.

FOR THE 'LOST CHILDREN'

There is a third group of children who, having recovered from what would be categorised as 'minor' head injuries, are discharged from follow up. There is growing concern that some of these children 'in fact suffer from specific cognitive deficits that significantly hamper their academic progress and life adjustment and that, in some cases, behavioural deterioration may occur long after injury.[6] Although there is good evidence that such minor injury can produce serious brain lesions, the extent of subsequent problems is as yet unknown.[9 10] It has always been difficult to assess premorbid functioning retrospectively, even in adults, and this difficulty becomes greater in younger, and therefore less well documented, children. It would be unrealistic to suggest detailed assessment and follow up of all cases of minor head injury, but community paediatricians have the network to inform parents and those professional people who come into contact with children in the community of the nature of potential problems, the diverse ways in which they may present, and how to obtain help.

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LETTERS TO THE EDITOR

Terminology in community child health—an urgent need for consensus?

SIR,—Annotations in *Archives* should not be ignored; perhaps that is what makes Dr Stone's semantic agonising,[1] ostensibly on behalf of community child health, so irritating. His suggested consensus on terminology is probably unattainable. It was ever thus: what on earth makes Dr Stone think that 'ambiguous technical language' is peculiar to community paediatrics?

Such an 'urgent' consensus is not even wholly desirable. We should certainly invoke Humpty Dumpty's rule of word usage—'when *I* use a word, it means just what I choose it to mean, neither more nor less'. Provided that people define their use of terms and are precise, differences of meaning, emphasis, and nuance which emerge can be useful catalysts of constructive debate.

Whatever the merits of Dr Stone's proposed definitions, his view of community child health is weird, his use of expressions such as 'terminological impasse', 'chronic linguistic malaise', and 'outdated and misleading jargon' is unhelpful, and his conclusions are frankly silly. Community child health does not suffer from 'chronic linguistic malaise', but from the effects of the 'professional and organisational vacuum' within which it has hitherto had to operate (I certainly agree about that). It also suffers from the failure so far to grasp and act upon the organisational and staffing implications of what a consultant led service really means.

If community child health did not already exist, something like it would need to be invented to fill the 'intermediate position between hospital based therapeutic paediatrics, and community based public health', which Dr Stone describes as uncomfortable, but which is in fact extremely stimulating, highly relevant to the health needs of children, and of potential benefit to all three disciplines.

As an academic community paediatrician I dissociate myself completely from Dr Stone's concluding remarks, particularly the 'we' referred to, whoever they may be. Community child health does not need to be dragged anywhere. It has momentum and a sense of direction, and community paediatricians are well aware of the reality of children's health needs in the community. I am confident that precision in terminology will also improve as we continue to focus on the practical issues involved. Semantics should never become a preoccupation.

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[1] Stone DH. Terminology in community child health—an urgent need for consensus. *Arch Dis Child* 1990;**65**:817–8.

Pathogenesis and management of aspergillosis in cystic fibrosis

SIR,—It is always a pleasure to read the lucid expositions produced in the papers of Dr Hiller. The annotation is timely and deals with a recurrent problem.[1] Unfortunately we would like to take issue with certain assertions made by Dr Hiller from the basis of the accumulated experience of the Bristol Cystic Fibrosis Clinic which one of the authors (FC) has run for the last 17 years. This clinical practice is rather similar to Dr Hiller's; currently our centre has 90 patients attending with cystic fibrosis. In Bristol a convincing case of bronchopulmonary aspergillosis producing lung damage has not been found. This does not imply that the possibility of making the diagnosis has not been enthusiastically pursued in many patients, but years spent attempting to establish definitive cases after our first publication[2] have disillusioned us as to the correctness of the reported frequency of this syndrome. The frequency of diagnosis presumably decreases with the increase in rigor with which the diagnosis is established. The central bronchiectatic lesion produced in asthmatic subjects and said to be characteristic in that annotation has not been encountered despite the enthusiastic and extensive use of standard chest radiography, computed tomograms, and even magnetic resonance imaging. Accordingly we do not believe that 'allergic bronchopulmonary aspergillosis is possibly underdiagnosed'. It is interesting that Bristol has so little experience of this 'complication' because the centre is an enthusiastic utiliser of nebulised antibiotics and only rarely utilises corticosteroids yet both these factors could increase the prevalence of the 'disease'. The immune reaction pattern in patients with cystic fibrosis in Bristol has been reported.[3]

The review also asserts that 'the major problem in cystic fibrosis is allergic bronchopulmonary aspergillosis in which *tissue damage* is due to the immune reaction of the host'. That is not established. Our most recent study[4] reviews after 11 years the well documented patients who had positive immediate skin reactions to *Aspergillus fumigatus* as reported in our previous study. It is apparent from the figure showing forced expiratory volume in one second (FEV_1) that lung function deterioration has not been increased by the continuing presence of a positive skin test.

We would agree with Dr Hiller that at the present time the use of antifungal drugs is not warranted for such 'disease'. A multicentre trial of bronchopulmonary aspergillosis that has been proved on lung biopsy and using itraconazole or some other antifungal on a double blind basis would be required to establish the importance of even such a tissue based diagnosis.

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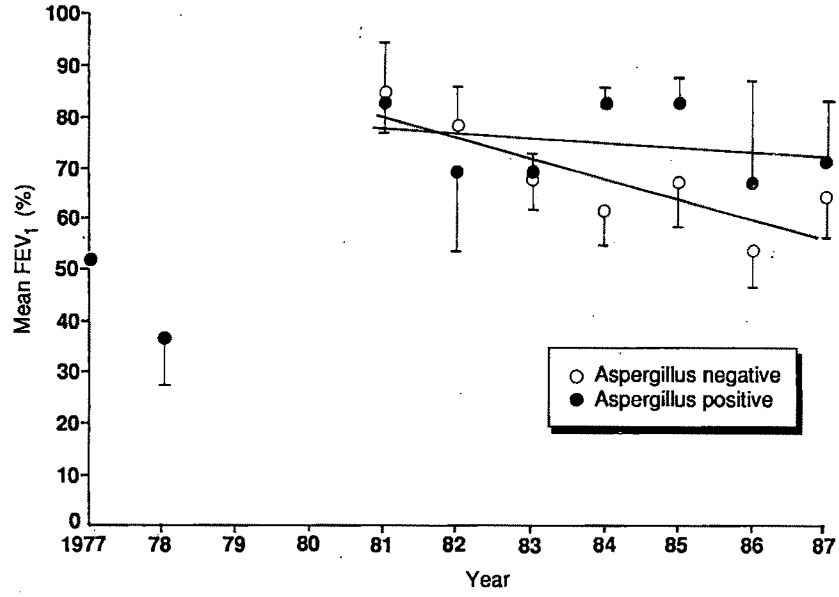

Deterioration in FEV_1 in patients related to whether skin test positive or negative for A fumigatus in 1977.

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Dr Hiller comments:

The incidence of diagnosed aspergillosis in cystic fibrosis clearly varies considerably, and the lack of cases in Bristol contrasts with the Leeds' experience published recently.[1] My statement that 'the major problem in cystic fibrosis is allergic bronchopulmonary aspergillosis in which tissue damage is due to the immune reaction of the host' is quoted out of context. I was discussing the different ways in which *Aspergillus fumigatus* can affect the lung, not the causes of lung damage in cystic fibrosis which are mainly the consequences of infection.

About one third of cystic fibrosis patients have a positive immediate skin test reaction to *A fumigatus*, as I described, and from the Bristol data this alone does not appear to be associated with a more rapid decline in FEV_1 than that seen in patients with a negative skin test, though the numbers of patients in each group is not given. A positive skin test indicates an IgE response. Total and specific IgE concentrations have been shown to have no correlation with clinical scores or lung function,[2] whereas IgG antibody showed close correlation with both. The nature of the immune response presumably determines the degree of tissue damage, and must vary in different individuals.

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DECEMBER 1990 VOL 65 NO 12

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Editorial

1289 Duplicate publication and related problems

Annotations

1291 Surgery for gastro-oesophageal reflux *E M Kiely*
1293 Atrial natriuretic factor: the heart as an endocrine organ *T J Stephenson, F Broughton Pipkin*
1295 Cold comfort for the catarrhal child *David Isaacs*

Original articles

1297 Roseola infantum and other syndromes associated with acute HHV6 infection *W L Irving, J Chang, D R Raymond, et al*
1301 HIV-1 infection in a cohort of haemophilic patients *N Wagner, R Bialek, H Radinger, et al*
1305 Rectal temperature of normal babies the night after first diphtheria, pertussis, and tetanus immunisation *D Rawson, S A Petersen, M P Wailoo*
1308 Factors influencing the body temperature of 3–4 month old infants at home during the day *E S Anderson, S A Petersen, M P Wailoo*
1311 Abnormal small bowel permeability and duodenitis in recurrent abdominal pain *S B van der Meer, P P Forget, J W Arends*
1315 Growth velocity before sudden infant death *S M Williams, B J Taylor, R P K Ford, et al*
1319 Increasing asthma prevalence in a rural New Zealand adolescent population: 1975–89 *R A Shaw, J Crane, T V O'Donnell, et al*
1324 Long term outcome of ventilated asthmatics *P C Seddon, D P Heaf*
Commentary *Margaret A Branthwaite*
1329 Cerebral palsy: why we must plan for survival *P M Evans, S J W Evans, E Alberman*
1334 Human isophane or lente insulin? A double blind crossover trial in insulin dependent diabetes mellitus *D M Gibb, A B M Foot, B May, et al*
1338 Microbiological studies of the enterocolitis of Hirschsprung's disease *D Wilson-Storey, W G Scobie, K G McGenity*
1340 The reliability of height measurement (The Wessex Growth Study) *L D Voss, B J R Bailey, K Cumming, et al*
1345 Are measurements of height made by health visitors sufficiently accurate for routine screening of growth? *M L Ahmed, P L Yudkin, J A MacFarlane, et al*
1349 Psychological characteristics of children with Shwachman syndrome *A Kent, G H Murphy, P Milla*
1353 Increase in serum concentrations of IgG$_2$ and IgG$_4$ by selenium supplementation in children with Down's syndrome *G Annerén, C G M Magnusson, S L Nordvall*
1356 Late deaths after treatment for childhood cancer *M M Hawkins, J E Kingston, L M Kinnier Wilson*
1364 Diagnosis of Pneumocystis carinii pneumonia from non-invasive sampling of respiratory secretions *R A Hague, S E Burns, J Y Q Mok, et al*
1365 Cystic fibrosis, Pseudomonas aeruginosa, and selective decontamination *A Mark Dalzell, Hendrik K F van Saene, David P Heaf*
1367 Nocturnal faecal soiling and anal masturbation *A F Clark, P J Tayler, S R Bhate*

Current topic

1369 Retinal haemorrhages *Baljit Kaur, David Taylor*

Personal practice

1373 Development of a psychiatric liaison service *D Black, A McFadyen, G Broster*
1376 **Referees and staff**
1378 **Letters to the editor**
1381 **Book reviews**
1385 **Index**

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ARCHIVES OF
DISEASE IN
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The Journal of the British Paediatric Association

Editorial

Duplicate publication and related problems

The editors of several international general paediatric journals have been concerned about two problems that weaken the quality of papers submitted for publication. One is the duplication of data in papers submitted to several journals, a practice known as self plagiarism.[1] The other is the practice of dividing a study up into numerous short reports; this results in what has been called the 'least publishable unit'.[2] Commonly, these submissions are presented simultaneously to different journals. We suspect that these practices are based on the desire to expand one's list of publications so as to enhance one's reputation and the chances of achieving promotion and academic tenure. In an effort to discourage these practices, the editors of the general American paediatric journals began some years ago to inform one another when they encountered examples of duplicate publication. Editors of European paediatric journals expressed interest in joining this informal network. We offer this collective statement primarily in the hope of discouraging this unnecessary proliferation of articles. We believe that more comprehensive reports will make *more* substantive additions to the paediatric literature.

We remind authors that when papers are submitted for consideration, they must be accompanied by assurances that the work is original and has not, or will not, be submitted elsewhere. In many instances over the last few years, we have received papers from authors who, in our opinion, violated the spirit and the intent of the copyright assignment. We recognise that there can be differences of opinion about the degree of overlap among papers. However, the editor must be informed when similar papers are submitted to more than one journal, and copies of the potentially overlapping manuscripts should be provided. In this way, referees and editors can make a judgment on the issue of duplication. Certainly, the existence of such papers should be indicated by referring to them in the text and listing them among the references. However, by common agreement, presentations at a scientific meeting or submitting an abstract to such a meeting does not constitute duplicate publication, even if the abstracts are to be published. The undersigned editors will continue to inform one another whenever they encounter examples of duplicate publication.

The issue of dividing a study into multiple components containing data that are somewhat different is more difficult because judgment is required to determine when the practice exceeds appropriate bounds. Investigators may feel justified to submit periodic progress reports of their research as information is developed. The test of appropriateness for this practice is the amount of new information provided by a separate publication. It is rarely justifiable to produce multiple papers on different aspects of a single study when the data have been collected over the same period of time; the amount of duplication among the introduction, methods, discussion, and references is usually very great, and we suspect that most authors recognise the problem because the papers are often submitted almost simultaneously to different journals.

A major problem caused by this form of duplicate publication is the 'wasting' of editorial pages. Each journal has a limited number of pages, and duplication of any type means that some papers are not published. Consolidation of small, related papers would enable more authors' work to be published in our journals. Editors should be made aware of such closely related papers, and be provided with a copy of them when that seems appropriate. As in the case of potentially overlapping manuscripts, examples of this practice will be shared with the other editors when they are recognised by one of us.

Another and possibly related concern has been the proliferation of journals,[1] which has made it more difficult for paediatricians to keep up with the literature. Indeed, there now is a secondary proliferation of journals designed to deal with the overload by summarising selected publications from the large number printed. During the past 15 years, more than 20 new paediatric publications have been instituted, and they total almost 10 thousand pages each year. We all recognise that the knowledge base is expanding rapidly, but we cannot help but wonder whether there is a need for so many journals, particularly when the number of papers being submitted to many established journals is not increasing significantly.[3] There is justification for some subspecialty publications, of course, but we believe that the availability of so many pages will inevitably result in a decline in overall quality of accepted manuscripts, based on the need to fill the pages of the many publications, new and old. We do not fear the 'competition' of these journals; rather, we believe that the information overload will reduce the quality of the product and discourage the average physician from even attempting to keep up.

We hope that these comments will be helpful to contributors to the general paediatric journals and will be seen as they are intended—as a constructive effort to maintain the quality of the paediatric literature. All of us believe that the reading of journals should be the fundamental method of continuing medical education for physicians. If that is true, all paediatricians will be benefited by a reduction in the quantity and improvement of the quality of what is published.

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Archives of Disease in Childhood 1990; **65**: 1291–1292

Annotations

Surgery for gastro-oesophageal reflux

Surgery for gastro-oesophageal reflux is becoming more popular. Figures from the United States show a rapid increase in the number of children undergoing such operations. From Oklahoma, Tunnell *et al* report two antireflux procedures in 1977 and 48 operations in 1981.[1] Similar large series are reported from other American centres, but there are no comparable publications from the United Kingdom.[2 3] Discussion with paediatric medical and surgical colleagues in this country revealed widely differing attitudes towards antireflux treatment with the emphasis on avoiding surgery. There is further disagreement on both the timing and choice of operation. The studies of Carré have had a lasting influence in this country. His publications, however, are confined to the management of patients with an established hiatus hernia associated with gastro-oesophageal reflux.[4 5]

Indications for operation

Surgery is indicated when non-operative measures have failed or are inappropriate. Only a very small number of children with reflux will come to operation. In general, surgery is undertaken for the complications rather than the presence of reflux:

(1) Apparent life threatening events (near miss sudden infant death syndrome) associated with confirmed gastro-oesophageal reflux is probably an absolute indication for surgery.[6 7] Failure of conservative management under these circumstances may be a dead baby. Investigation of a group of such infants has shown that many have an atypical pattern of reflux with a predominance of reflux during sleep.[8]

(2) Failure to thrive in association with persistent vomiting is primarily a problem of young infants. Failure to respond to a three to four week course of conservative management raises the question of surgery. Although operation may ease feeding problems and allow an adequate energy intake, the coexistence of other causes of growth retardation may prejudice the outcome.

(3) Respiratory complications of reflux, such as recurrent pneumonia and asthma, constitute a major indication for surgery in older children.[2 9]

(4) Oesophagitis and stricture are considered the result of severe reflux with poor acid clearance. The incidence of stricture varies in different surgical series and the issue is further confused by the addition of children with repaired oesophageal atresia. Figures quoted vary from 1·4 to over 40% with a lower incidence in more recent publications.[9–13] Surgery is the most effective treatment for permanent cure of stricture.

(5) Severe gastro-oesophageal reflux is common in severely retarded or brain damaged children.[14] Surgery may be required for failure of medical treatment, to relieve oesophagitis or stricture, or for overwhelming social reasons.[9 15 16] Gastrostomy is often a useful addition to facilitate feeding in these children.[16]

Antireflux surgery

Antireflux operations are designed to reinforce the natural antireflux mechanisms. The aims are to repair the oesophageal hiatus, to increase the length of intra-abdominal oesophagus, and to restore an acute angle of His (between oesophagus and fundus).[17 18] The procedures most commonly employed in children are the Nissen and Thal operations.[1 2 19–21]

In the Nissen operation, the lower oesophagus is enclosed in a 360° fundal wrap. The result is a one way valve which abolishes reflux, belching, and vomiting. These effects are often permanent.

In the Thal operation, and its variants, a 180°–270° fundal wrap is performed. This is effective in abolishing reflux but preserves the ability to belch and vomit.

Both procedures are generally performed through an abdominal approach.

Complications of surgery

Operative deaths are uncommon: 1·4% in a large postal survey.[21] Large modern series quote a 0% operative mortality. However, there is a substantial late death rate of 16–24% from pre-existing conditions or later adhesion obstruction.[1 2 21 22] The dangers of adhesion obstruction in a child who cannot vomit are obvious to the initiated. Adhesion obstruction rates vary from 0·9 to 10% in published series.[1 3 22]

Morbidity directly related to the fundoplication include recurrent hiatus hernia, wrap disruption, gas bloat, recurrent gastro-oesophageal reflux, and dysphagia. Turnage *et al* report that 43% of their patients undergoing fundoplication had at least one postoperative complication and 12% required reoperation.[2] These results seem broadly representative.

The Thal operation seems to be associated with fewer complications and fewer repeat operations.[3] Despite these figures, however, this operation has not yet gained wide acceptance.

A clinical diagnosis of dumping syndrome was made in 8·5% of my own patients but curiously, this problem receives scant attention in the literature. Ashcraft reports transient postoperative diarrhoea in some of his patients, which may be a similar problem.[3]

Results of surgery

Relief of symptoms is usual if symptoms have been due to gastro-oesophageal reflux. Satisfactory results are reported in 74–94%.[1 2 3 10] Of the different groups undergoing surgery, the results are often most gratifying in severely retarded children. They may be rendered pain free for the first time in their lives. Unfortunately, surgery in these children is associated with the highest complication rate.[23]

Conclusions

Antireflux surgery has become popular for very good reasons. The underlying pathophysiology is not understood in the majority of children.

Treatment to control reflux, whether medical or surgical, is primarily to alleviate the complications of reflux rather than to abolish the cause of reflux. Surgery is extremely effective in abolishing reflux but potential postoperative problems rightly limit its use to only a minority of patients.

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Atrial natriuretic factor: the heart as an endocrine organ

It has been known for some years that secretory granules exist within atrial myocytes, that the density of these granules is altered by changes in fluid balance, and that distention of the atria induces diuresis and natriuresis, and suppresses release of renin, aldosterone, and vasopressin. With the discovery that extracts of cardiac atria contain a potent natriuretic factor (ANF), that the granules are the storage site for ANF, and that atrial distention provokes ANF release, it became clear that the atria have both afferent and efferent functions in circulatory homoeostasis.[1] However, ANF is not de Wardener's 'third factor'.

ANF is a 28 amino acid peptide which is released after cleavage of a 126 amino acid storage precursor and has a half life of 2–3 minutes. The only definite sources of circulating ANF are the cardiac atria but ANF also appears to be present in lung, brain, and fetal cardiac ventricles.

ANF release is stimulated by atrial distention, increase in intravascular volume, increased atrial pressure, and dietary sodium loading.[2] ANF release is also provoked by infusion of α adrenergic agonists, angiotensin II, and antidiuretic hormone.[1] ANF acts via a 'second messenger', cyclic guanosine monophosphate.

Actions of atrial natriuretic factor

Caution is needed here because of the unphysiological doses of ANF used in many studies. Studies in animals and adult man show that ANF has endocrine, renal, and vasomotor actions. Not only does ANF directly inhibit release of renin, aldosterone, and antidiuretic hormone,[3 4] but ANF also antagonises the target organ effects of angiotensin II and antidiuretic hormone.[1] As a result of these actions and of a paradoxical constrictive effect on the glomerular efferent arteriole, ANF causes an increase in glomerular filtration rate, and a diuresis and natriuresis. These actions suggest that antagonism of the renin-angiotensin-aldosterone system may represent a major function of ANF.

ANF administration is associated with a variable decrease in systemic blood pressure and a transient increase in regional blood flow to kidneys, lung, and myocardium.[1] ANF attenuates the pulmonary vasoconstriction induced by hypoxia[5] and may act as a bronchodilator.[6] ANF also induces a shift of fluid from the vascular to the extravascular space, possibly by increasing capillary leakiness.[7] Finally, ANF may function as a neurotransmitter peptide and has direct effects on the central nervous system such as the inhibition of thirst.[1 4]

Atrial natriuretic factor in the fetus

Fetal umbilical arterial ANF concentrations are not correlated with maternal concentrations and are the same or slightly higher.[8] Umbilical artery ANF concentration is significantly greater than umbilical vein concentration,[9] suggesting that the placenta consumes or takes up ANF. The human placenta has ANF binding sites and there is some evidence of a placental barrier to ANF transfer.[10]

ANF concentrations increased appropriately in response to hypervolaemia,[11] and decreased with haemorrhage (R A Brace, C Y Cheung, personal communication) in the sheep fetus. In this model, fetal ANF also increased in response to hypoxia,[11] which may be significant in view of the pulmonary vasodilator actions of ANF,[5] and fetal urine production increased in response to ANF. ANF concentrations were significantly raised in human fetuses undergoing cordocentesis for Rhesus isoimmunisation at 28 weeks' gestation, and the ANF concentrations increase further after intrauterine transfusion.[8] This suggests that in the human fetus, at least by the third trimester, ANF concentrations increase with pathological or iatrogenic volume expansion. Fetal ANF may also increase umbilical blood flow,[12] and a decreased density of ANF receptors has been reported in placentas from pregnancies complicated by intrauterine growth retardation.

Atrial natriuretic factor in the newborn

The changes in right atrial pressure, glomerular filtration rate, and fluid balance that occur in the immediate postnatal period in normal term infants would suggest that ANF may have a physiological role.[13] ANF may also have a role in respiratory illness as a diuresis occurs during the recovery phase of respiratory distress syndrome, and failure of such a diuresis may be predictive of the later development of bronchopulmonary dysplasia.

Normal values for ANF concentrations show no age variation beyond the neonatal period.[9 14] ANF concentrations are only slightly raised in cord blood compared with later life,[15] but they increase dramatically over the first few days in normal term infants and remain high throughout the first week of postnatal life.[9 14 15] Although this increase in plasma ANF mirrors the course of postnatal negative salt and water balance,[13] there was no correlation between ANF concentrations and urine sodium excretion.[15] Dietary salt loading of premature infants increases plasma ANF,[16] and this perhaps explains why previous attempts at manipulating intake to prevent early postnatal hyponatraemia have failed.

In premature infants with respiratory distress syndrome, we have also observed a significant increase in ANF concentrations over the first few days of life (T Stephenson, F Broughton Pipkin, D Hetmanski, unpublished observations), and they are higher the more severe the respiratory distress[17] and highest during the diuretic phase of the illness.[18] The ANF concentrations observed in these premature infants are much higher than in healthy term infants and yet, despite this, renin concentrations are also very high in the early postnatal period.[19] Persistence of high ANF and antidiuretic hormone concentrations beyond early postnatal life may be associated with bronchopulmonary dysplasia.[20]

Atrial natriuretic factor and cardiac disease in childhood

In the premature infant, plasma ANF concentrations were raised in the presence of a patent ductus arteriosus[21] and fell with surgical ligation. In neonates with transposition of the great vessels, plasma ANF concentration correlated with left atrial pressure and ANF fell after septostomy.[22] In older children with heart failure, the concentrations were above the normal range[14 23] and fell after treatment.[23] These authors suggested that ANF may be useful in the treatment of heart failure, as it may reduce both preload and afterload.

In children with septal defects, ANF concentrations were also increased and correlated with shunt size.[23] Davis *et al* found that atrial pacing in children increased plasma ANF concentrations, although atrial pressure was unchanged, the increase in ANF being related to the increase in rate.[24] This is consistent with the diuresis which follows episodes of supraventricular tachycardia.

Atrial natriuretic factor and renal disease in childhood

Normotensive children on maintenance haemodialysis have predialysis ANF concentrations which are significantly higher than ANF concentrations in normal children or children with advanced renal failure but no volume expansion.[25] Plasma concentrations fell significantly during haemodialysis and the magnitude of this fall was directly related to the fall in body weight during dialysis.[24] In animal models, prompt 'rescue' infusion of ANF after either noradrenaline or gentamicin induced renal failure significantly improved glomerular filtration rate, urine volume, and sodium excretion.[2]

Hypertension

In essential hypertension, ANF concentrations were normal in childhood but raised by adolescence.[26] Whereas plasma ANF correlated with fractional and 24 hour urinary excretion of sodium in matched normotensive controls, no correlation was found in the smaller number of hypertensives. An impaired ANF response to high dietary salt intake has been reported in the offspring of hypertensive parents.[27] These two studies suggest that in childhood essential hypertension, the contribution of ANF to sodium balance may be abnormal and this may help to clarify the complex pathogenesis and familial clustering of this condition.

Metabolic disorders

It has been suggested that Bartter's syndrome may be a 'syndrome of inappropriate ANF secretion' (as these patients are volume contracted),[28] but the raised ANF concentration may also be secondary. Gordon's syndrome may result from end organ insensitivity to ANF.[28] ANF concentrations are increased in adults with endogenous or exogenous glucocorticoid excess[2] and primary hyperaldosteronism[28] and ANF falls to normal with treatment.

Summary

The growth in understanding about ANF over the last 10 years reflects the pace of modern biological research. Within three years of the initial report that atrial extract contained a natriuretic factor, human ANF was purified, sequenced, and cloned. Atrial dimension is the major determinant of ANF release, ANF has natriuretic and vasodilator effects, and ANF has a definite role in response to an acute increase in intravascular volume. It is not yet clear how important ANF is in the regulation of sodium and water balance and blood pressure under steady state, physiological conditions.

Most of our understanding is derived from experimental studies in animal models or from observational studies in adult man. The production of ANF by biotechnology allows interventional studies, however, and further advances may be made if specific antagonists of ANF can be developed. ANF may have therapeutic potential in the treatment of heart failure, respiratory distress syndrome, acute renal failure, oedema and ascites, systemic and pulmonary hypertension, and asthma. ANF anatgonists might prevent hyponatraemia of prematurity and alleviate Bartter's syndrome. ANF is not nephrotoxic and is without many of the side effects of current diuretics and vasodilators but its use is currently limited by the very short half life and the need for intravascular administration.

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Cold comfort for the catarrhal child

John Fry coined the phrase 'the catarrhal child' to describe the child we all know only too well with ever running nose whose desperate mother begs us to do something to staunch the flow of mucus. An understanding of the epidemiology and pathogenesis of upper respiratory tract viral infections may not enable us to stop the nose from running, but it can help us not to prescribe valueless medications and not to investigate the children unnecessarily.

Respiratory viruses

Children experience more respiratory virus infections than adults because their secretory immune system is relatively immature, because they have not encountered the viruses before, and because they are exposed to more such viruses than most adults. There are over 100 strains of rhinovirus, and infection with one strain provides little or no cross protection against infection with a different strain. Coronaviruses are another important cause of upper and lower respiratory tract infections in preschool children.[1] Other viruses that can cause childhood respiratory infections include parainfluenza viruses, influenza viruses, adenoviruses, and enteroviruses. Respiratory syncytial virus not only causes bronchiolitis in infancy, but older children can be reinfected every winter, with successively milder infections, which can nevertheless result in otitis media or a febrile cold with coryza, cough, and sore throat.[2]

Epidemiology

Recurrent respiratory tract infections are normal in the first few years of life. Maternal antibody gives relative protection for the first three to six months and breast feeding also protects against respiratory viruses but, as passively acquired antibody wanes, the child becomes more susceptible to respiratory infections. These comprise about 85% of childhood infections.[3]

The number of infections experienced by each child depends on several factors of which the most important is probably the intensity of exposure to respiratory viruses. In an important longitudinal study of childhood infections in Cleveland, Ohio, Dingle *et al* found that children under 5 years old who attended nursery school had on average 12 respiratory infections per year.[4] Children of the same age not attending school but with a sibling at school had a mean of nine infections per year, while children of the same age not at school and with no sibling at school had six to seven infections annually. Day care attendance results in an increased incidence of respiratory infections.[5 6] If children attend day care in the first year of life, then this becomes the year in which they experience most respiratory infections.[6] The average preschool child will have six to eight respiratory tract infections a year in their preschool years, with the maximum incidence from 2 to 4 years of age.[3 4]

Urban children experience more respiratory infections than rural children, probably due to increased exposure. Maternal smoking is an important factor in determining the incidence of childhood respiratory infections,[5] and if parents cannot be persuaded to stop smoking they should at least be prevailed upon to smoke outdoors.

Infections tend to be more frequent in the winter months, although parainfluenza virus infections occur mainly in the summer and enterovirus infections in the late summer and early autumn, so that a child can have infections most of the year. In a longitudinal cohort study of children with recurrent respiratory tract infections, many of whom conformed admirably to John Fry's description of the catarrhal child, we found that children would develop rhinitis due to a proved respiratory viral infection with a clear nasal discharge which rapidly became mucopurulent. The nasal discharge would last 10 to 14 days, dry up for a day or two, then the child would be infected by a different virus and the process would recommence.[7] Thus a superficial appearance of continuous rhinitis was in fact due to recurrent viral infections. Mucopurulent nasal discharge does not imply bacterial superinfection, as it is commonly seen in colds with little or no change in bacterial flora,[7 8] and antibiotics are not indicated unless the child has an additional indication such as otitis media.

Pathophysiology

The nasal secretions in rhinorrhoea contain a number of proteins. Mucous glycoproteins are secreted by goblet cells and by serous and mucous glandular cells in the submucosal glands. Albumin is synthesised in the liver, circulates as a vascular protein, and diffuses into glandular secretions passively when vascular permeability increases.[9 10] Monomeric IgA is synthesised by plasma cells restricted to the periglandular region.[10] Secretory component is made by serous cells in the seromucous glands. Secretory IgA, two molecules of IgA linked together by a joining (J) chain and secretory component, is solely a glandular product.[10 11] Interferon beta is produced by nasal fibroblasts in response to viral infection while local interferon alfa is produced by lymphocytes and probably by a number of other types of nucleated cell.[12 13]

Rhinoviruses cause little damage to the nasal epithelium during colds[14 15] so it is probable that coryzal symptoms are largely due to inflammatory mediators. Nasal provocation tests performed on normal and atopic adults using histamine and the cholinergic drug methacholine suggest that secretory IgA secretion may be under cholinergic control,[10] whereas histamine increases plasma protein extravasation, stimulates glandular secretion,[16] and increases the proportion of IgG in nasal secretions.[17] Nasal provocation tests only examine the response to a single exogenous substance, a very unphysiological situation, and their relevance to what occurs in an infection is doubtful.

Naclerio and colleagues measured concentrations of inflammatory mediators in nasal secretions of young adults during experimental rhinovirus colds.[18] They found that nasal concentrations of histamine did not increase during colds, whereas volunteers who became symptomatic had a considerable rise in nasal concentrations of bradykinin and related kinins. They postulated that kinins, particularly bradykinin, might be responsible for the symptoms of rhinovirus colds. Trials of antihistamines have shown little or no benefit in alleviating the symptoms of colds,[19 20] and Naclerio *et al* suggested the development and study of kinin antagonists.

Another possible candidate for causing some of the symptoms of colds is interferon. When interferon alfa is injected into volunteers it causes flu like symptoms such as fever, malaise, headache, and myalgia.[21] During viraemic infections interferon alfa can be detected in the serum[22] and interferon may be responsible for some of the systemic effects of viraemic respiratory infections such as influenza.

Local administration of interferon by nasal spray often causes nasal stuffiness, congestion, mild epistaxis, and sore throat within a few days.[23] Interferon is probably not the sole cause of the nasal symptoms of colds, however, as respiratory syncytial virus causes rhinorrhoea and sore throat in adult volunteers who do not mount a significant nasal or systemic interferon response to infection with this virus.[24]

Investigation of recurrent respiratory infections

Parental anxiety is a common reason for children presenting to general practitioners and paediatricians with 'too many' respiratory infections. If the doctor is satisfied, after taking a history, that the child is experiencing no more than his or her expected quota of viral respiratory infections, reassurance of the parents will usually quell the anxiety. Persistent anxiety indicates that either the child or the parents has a real problem.

Localisation of signs and symptoms to a single site is suggestive of an anatomical cause. For example unilateral mucopurulent nasal discharge may be due to a foreign body or a unilateral choanal atresia. Recurrent lower respiratory tract infections may be due to a number of different causes outside the scope of this annotation, and require further investigation.

Allergic rhinitis may cause seasonal or perennial rhinitis,[25] and this is an important differential diagnosis for the child with suspected recurrent upper respiratory tract infections. There may be a history of nasal symptoms in association with exposure to potential allergens such as feathers, house dust, grass, or other pollens. This is not always present but can give a useful lead. In allergic rhinitis the child often has other atopic diseases, with asthma particularly common,[25] or there is a family history of atopy. Nasal stuffiness, sneezing, and itching of the nose are often more troublesome than rhinitis. Nasal smears should be examined for mast cells as their presence is a more specific and more sensitive test of allergic rhinitis than the presence of eosinophils.[25]

Children with recurrent upper respiratory tract infections should probably be investigated for immune deficiency only if there are features of their infections or additional factors to suggest such a problem. Recurrent acute otitis media may be due to recurrent viral or bacterial infections which, unless tympanotomy is performed as is routine in some parts of Europe, cannot be distinguished easily. Chronic or recurrent purulent ear discharge is suggestive of recurrent bacterial infections and of immune deficiency. Hypogammaglobulinaemia may present in this way, as may IgG subclass deficiency, particularly IgG_2 deficiency. As total serum IgG concentrations are often in the normal range in children with IgG_2 subclass deficiency, it is wise to measure total serum immunoglobulin and IgG subclass concentrations in children with recurrent otitis media, particularly when there is purulent otorrhoea.

A family history of recurrent or severe infections may be an important clue to immune deficiency. Persistent candidiasis, particularly if there is nail as well as oral involvement (mucocutaneous candidiasis), is suggestive of defective T lymphocyte function. Infections with opportunist organisms such as *Pneumocystis carinii* or nocardia almost certainly indicate a profound T cell defect, as do severe infections with certain common viruses such as giant cell pneumonia from measles or haemorrhagic chickenpox.

Treatment

Osler stated 'there is just one way to treat a cold and that is with contempt'. No medicine has yet proved to be significantly more effective, and a number of remedies for colds and catarrh are potentially harmful. Unnecessary antibiotics should be avoided, as should antihistamines, decongestants, and cough suppressants. Most children with recurrent infections eventually grow out of them, a truism of some modest comfort to the beleaguered parents.

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ORIGINAL ARTICLES

Roseola infantum and other syndromes associated with acute HHV6 infection

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Abstract

Eight cases of acute human herpesvirus type 6 (HHV6) infection in infants were diagnosed serologically by the demonstration of IgM anti-HHV6 (8/8) and a significant change in total anti-HHV6 antibody titre (6/8). Four infants were sufficiently ill to require admission to hospital and further investigations: one with encephalitis and three with gross hepatosplenomegaly, two of whom had evidence of simultaneous infection with another herpesvirus. The remaining four infants had an illness compatible with roseola infantum, although this diagnosis had not been made clinically. Sera from two of those infants with rash had been sent for analysis to exclude rubella because the infants' mothers were pregnant. The other two had received antibiotics when febrile, and the subsequent appearance of the roseola rash had raised the possibility of antibiotic allergy.

The data suggest that there are clinical syndromes in addition to roseola infantum associated with the presence of IgM anti-HHV6, in which serological screening for evidence of acute HHV6 infection may be useful.

Human herpesvirus type 6 (HHV6) is a recently identified human lymphotropic virus of diverse cell tropism in vitro.[1–3] Serological surveys have shown a high prevalence of antibodies to HHV6, and have suggested that the majority of HHV6 infections occur in the first year of life.[4–6] Descriptions of clinical illness in infants associated with seroconversion to HHV6 are limited to the syndrome of roseola infantum (also known as exanthem subitum), two infants with a rash and lymphadenopathy and two infants with a hepatitic illness, one fatal.[6–9] There are additional reports of acute HHV6 infection in older children and adults associated with hepatitic and infectious mononucleosis like illnesses.[10 11]

In order to identify possible clinical consequences of acute HHV6 infections we have devised a strategy for screening sera for the presence of IgM anti-HHV6.[10] This has been applied to sera from infants presenting with a variety of illnesses, resulting in the identification of eight acute HHV6 infections, none of which had been diagnosed clinically as roseola infantum. The clinical features of those eight infants described here illustrate that HHV6 serology may be useful in the investigation of infants with encephalitis or hepatosplenomegaly, in the investigation of a rash in an infant whose mother is pregnant, and to exclude either the need to prescribe antibiotics in a febrile child, or the diagnosis of antibiotic allergy.

Methods

SELECTION OF SERA

During the course of this study (December 1988 to February 1990) all sera sent to the virology laboratory, Westmead Hospital, from infants up to the age of 3 years were tested for evidence of recent HHV6 infection. In addition, sera from infants presenting with hepatosplenomegaly were kindly referred to us from the Royal Alexandra Hospital for Children, Sydney, the Royal Children's Hospital, Melbourne, and the Royal Brisbane Hospital, Brisbane. The infants fell into the following diagnostic categories (number of sera): neonates with jaundice, congenital abnormalities, or those labelled for screening for toxoplasma, other viruses, rubella, cytomegalovirus, and herpes virus (n=31); children with fever (n=6); rash (n=21); encephalitis (n=6); hepatomegaly and/or splenomegaly (n=10); glandular fever like illness (including tonsillitis, lymphadenopathy (n=17); clinical details not given (n=7); and miscellaneous (father carrier of hepatitis B virus, nephrotic syndrome, ?idiopathic thrombocytopenia, ?mumps, ?dengue (n=5).

SEROLOGY

Sera were screened by indirect immunofluorescence for the presence of IgM and IgG anti-HHV6 antibodies as previously described, using acetone fixed HHV6 infected J Jhan cells (a T cell line) as substrate.[10] Briefly, sera were screened at dilutions of 1/100 for IgG and 1/20 for IgM in phosphate buffered saline containing 1% casein. Screen positive sera were retested for IgM after a 1/10 dilution in an anti-IgG reagent (Gullsorb, Gull Laboratories) for absorption of IgG and removal of rheumatoid factor. Fluorescein conjugated second antibodies used were sheep antihuman immunoglobulin (Wellcome), and F(ab')$_2$ fragment goat antihuman IgM (Kallestad). No non-specific fluorescence was seen when sera were tested using acetone fixed uninfected J Jhan cells as a negative control.

Commercially available enzyme immunoassay kits were used for the detection of IgG and IgM anticytomegalovirus (Pharmacia), and IgG and IgM antirubella antibodies (Behring). IgM anti-Epstein-Barr virus was assayed using an in house enzyme immunoassay,[12] and IgG anti-Epstein-Barr virus by indirect immunofluorescence using Epstein-Barr virus infected

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Acute HHV6 infection in infants: serological data

Case No (sex)	*Age (months)*	*Illness*	*Date of serum sample (days)**	*HHV6*		*Cytomegalovirus*		*Epstein-Barr virus*			*Other negative serology*
				IgG†	*IgM*	*IgG*	*IgM*	*IgG*	*IgM*	*Epstein-Barr nuclear antigen*	
1 (F)	13	Encephalitis	0	1024	Positive		Negative				Herpes simplex virus,‡ mumps, mycoplasma, measles, enterovirus, varicella
			10	1024	Positive	Positive	Negative		Negative		
			24	512	Negative						
			185	256	Negative						
2 (M)	10	Hepatosplenomegaly	0	16	Negative	Negative	Negative				
			16	128	Positive	Negative	Negative		Negative		
			42	128	Negative						
3 (M)	6	Hepatosplenomegaly	0	8	Positive	Negative	Negative	2560	Negative§	Negative	
			14	2048	Positive	Negative	Negative	2560	Positive	Negative	
4 (M)	16	Hepatosplenomegaly	0	512	Positive	Equivocal	Positive	Positive	Negative		
			13	512	Positive						
5 (M)	12	Roseola infantum	0	8	Negative						Measles, adenovirus, enterovirus, rubella
			15	256	Positive	Negative	Negative		Negative		
6 (F)	8	Roseola infantum	0	8	Positive	Positive	Negative	Negative	Negative		Measles, rubella
			11	256	Positive	Positive	Negative	Negative	Negative		
7 (M)	19	Roseola infantum	0	<4	Positive	Negative	Negative	Negative	Negative		Measles
			27	64	Negative						
8 (F)	8	Roseola infantum	0	64	Positive						Measles, rubella
			7	128	Positive						

*Day 0 taken as the date of the first serum sample.
†Titre as determined by immunofluorescence.
‡Herpes simplex virus, complement fixation titre less than 4 in all samples.
§Epstein-Barr virus IgM negative by enzyme immunoassay but positive by fluorescence.

marmoset lymphoblastoid cells as substrate. Anti-Epstein-Barr nuclear antigen antibodies (anti-EBNA) were determined by an anticomplementary immunofluorescent technique.[13] All other antibody titres were assayed by a standard complement fixation test.

Results

Sera from eight patients were found to contain IgM anti-HHV6. The serological results are summarised in the table.

CASE REPORTS

Case 1

A 13 month old girl presented with right sided focal seizures. She had been unwell for one week, initially with rhinorrhoea and cough, and in the two days before admission became increasingly lethargic and began vomiting. Four right sided seizures with variable involvement of face, arm, and leg, each lasting less than 10 minutes, occurred on the morning of admission.

On examination she was drowsy and miserable, with a temperature of 37·9°C. A blotchy erythematous rash was present over her upper trunk. Her eyes tended to deviate to the left and there were signs of mild right sided weakness. Results of investigations were haemoglobin concentration 13 g/l, white cell count $15·1\times10^9$/l with 75% granulocytes and platelets 236×10^9/l. Serum electrolytes, blood glucose, calcium, magnesium, and phosphate concentrations were all normal. In the cerebrospinal fluid there was one polymorph, 14 mononuclear cells and 85 red blood cells $\times10^9$/l. Cerebrospinal fluid protein was 160 mg/l and glucose 5·5 mmol/l. Cerebral computed tomography showed loss of grey white differentiation in the left frontotemporal regions with loss of the sulcral pattern indicating mass effect. Electroencephalography showed pronounced slowing from the left hemisphere with high voltage 1/2–3 hertz activity appearing at times in a semiperiodic fashion.

She was treated with phenobarbitone (loading dose of 10 mg/kg followed by 5 mg/kg/24 hours) and acyclovir (10 mg/kg every eight hours for 10 days). No further seizures occurred and by 24 hours after admission her neurological state had returned to normal. She continued to spike temperatures up to 38·5°C over the next few days but otherwise completed her course of acyclovir without further problems. When last reviewed at age 19 months there were no definite neurological signs. She had been walking for three months and her parents stated she had a vocabulary of 50 words. Repeat computed tomography showed atrophic changes in the left frontotemporal region.

Case 2

This 10 month old boy had been admitted to hospital with a febrile fit and pneumonia, and then discharged. One week later he presented with a history of two days of fever followed by the appearance of a dense fine rubelliform rash over the limbs and trunk (but not face), 7 cm hepatomegaly and 4 cm splenomegaly, and shotty diffuse lymphadenopathy, none of which had been present during his hospital stay. A full blood count showed a haemoglobin concentration of 10·9 g/l, a leucocyte count of $12·6\times10^9$/l with a lymphocytosis of 55% and 26% atypical mononuclear cells. Liver function tests were normal. The rash lasted for 24 hours only. The cause of his hepatosplenomegaly remained unclear. His physical signs resolved slowly over the following three months, eventually disappearing completely.

Case 3

This 6 month old boy presented with fever and cervical lymphadenopathy 48 hours after triple antigen immunisation. Twenty four to 48 hours later he developed a fine rubelliform rash over the face and trunk, cervical lymphadenopathy, and mild splenomegaly. At this stage a full blood count showed a microcytic normochromic anaemia and neutropenia, with atypical mononuclear cells. His rash disappeared after 48 hours. Two days later he was admitted to hospital with hepatosplenomegaly, anaemia, neutropenia, and thrombocytopenia. Several investigations were performed to ascertain the cause of the child's illness, including bone marrow aspiration, but no diagnosis was reached. The physical signs and the abnormal haematology resolved spontaneously over a period of several months.

Case 4

This 16 month old boy presented with fever, respiratory distress, hepatosplenomegaly, and cervical lymphadenopathy. He was also noted to have a few petechial lesions over one cubital fossa, of 24 hours duration. A diagnosis of bronchopneumonia was made. A chest radiograph showed patchy consolidation throughout both lung fields which resolved within a week. Respiratory syncytial virus was isolated from a nasopharyngeal aspirate. Investigation of his hepatosplenomegaly included a full blood count (haemoglobin concentration 10·8 g/l, white cell count of $19{\cdot}2\times10^9$/l with 51% lymphocytes and 16% atypical mononuclear cells). Liver function tests were also performed and his aspartate aminotransferase activity was 80 U/l (normal range 15–55); γ-glutamyltransferase and bilirubin were normal. A diagnosis of cytomegalovirus infection was made on the basis of a positive IgM anticytomegalovirus assay and isolation of cytomegalovirus from a urine sample taken one week after presentation. He was well on review a month later, and no further mention has been made of hepatosplenomegaly on subsequent clinical examinations.

Case 5

This 12 month old boy was admitted to hospital with a two week history of rhinorrhoea and a dry cough, and 48 hours of fever (40°C). There was no lymphadenopathy, hepatomegaly, or splenomegaly noted. The fever settled spontaneously after a further 24 hours, and a rash noted 24 hours later. As his mother was six weeks pregnant, acute and convalescent serum samples were sent to the laboratory for rubella, measles, adenovirus, and enterovirus serology.

Case 6

This 8 month old girl presented with a mild fever and a rubelliform rash confined to the trunk, described as flat pink macules 3·5 mm in diameter, without crusting or excoriation. Mild cervical lymphadenopathy was noted, but no hepatomegaly or splenomegaly. The rash resolved after four days. Acute and convalescent sera were sent to the laboratory for rubella and measles serology as the child's mother was pregnant.

Case 7

This 19 month old boy presented with a four day history of fever (>38°C), cough, and sore throat. Mild cervical lymphadenopathy was noted. A provisional diagnosis of streptococcal pharyngitis was made, and penicillin prescribed. Forty eight hours later his fever was resolving, but a rubelliform rash was noted, ascribed to either measles virus infection, or to penicillin allergy. The rash lasted three to four days, by which time all other symptoms and signs had resolved.

Case 8

This 8 month old girl presented with an upper respiratory tract infection, treated with ampicillin and subsequently erythromycin. A morbilliform rash then developed, lasting four days. A convalescent serum was sent to the laboratory for measles serology.

SEROLOGY

IgM anti-HHV6 was demonstrated in at least one serum sample from each infant. In five of the infants it was also possible to demonstrate a rise in IgG anti-HHV6 titre in paired sera, while in two of the remaining three infants (cases 1 and 4), the titre in the acute serum was already raised. IgM anti-Epstein-Barr virus was detected only in sera from case 3, and IgM anticytomegalovirus only in sera from case 4. Additional negative serology from individual patients is given in the table.

Discussion

HHV6 has recently been identified as the causative agent of roseola infantum.[7] This disease is characterised by an abrupt onset of fever, which lasts three to five days before subsiding, when a maculopapular rash appears on the neck and trunk. The rash may be fleeting, or may not be detected at all.[14] Roseola is generally considered to be a benign disease, but it was suggested as long ago as 1949 that atypical, more severe forms of the disease may occur.[15]

While serological diagnosis of herpesvirus infections may not be able to distinguish between primary and reactivated infections with such viruses, it is most likely that the presence of IgM anti-HHV6 in sera from infants in the first two years of life is indicative of primary infection. Thus we believe that the eight infants described in this paper had indeed suffered recent HHV6 infections.

Four of the infants we report had severe illnesses requiring admission to hospital, temporally related to the presence of IgM anti-HHV6 (4/4) and rising titres of IgG anti-HHV6 (2/4) in their sera. Case 1 was suspected of having herpes simplex encephalitis, and treated accordingly with acyclovir. However, her illness was unusually mild for this disease, and she failed to develop any antibodies to herpes simplex virus in a serum sample taken seven months after her illness. In addition, she had serological evidence of a recent HHV6 infection, as well as a rash consistent with roseola infantum, and it is likely that her encephalitic illness was related to this. Convulsions are well recognised as a common occurrence in roseola infantum, and there are several reports of transient (stupor, coma, hemiparesis, bulging fontanelles) and permanent (hemiparesis) neurological sequelae of the disease.[16–20] The authors of those reports raised the possibility of a 'specific encephalitis due to the roseola virus', although in the absence of an identifiable causative agent none were able to substantiate the hypothesis. Prospective diagnosis of similar cases, both serologically and by virus isolation, should finally allow proof of those astute clinical observations.

The predominant feature of the illness in cases 2–4 was hepatosplenomegaly. This has not, to our knowledge, been reported previously in either roseola infantum or in acute HHV6 infection, although there are two reports of hepatitis in infants, one fulminant and fatal, due to HHV6 infection.[8 9] All three infants had a fleeting rash, noted to appear after defervescence in cases 2 and 3. The diagnosis of roseola infantum due to acute HHV6 infection seems to be clearcut in case 2. The simultaneous appearance of IgM anti-Epstein-Barr virus or anticytomegalovirus in cases 3 and 4, however, make their diagnoses more problematic. The presence of dual antibody rises to HHV6 and cytomegalovirus has been noted previously,[21] and we have shown that such dual rises are not due to cross reactive antibodies.[22] Dual primary infections, primary infection with one virus plus reactivation of the second virus, or dual reactivations are all theoretical possibilities. The age of case 3 (6 months), the very low concentration of IgG anti-HHV6 in his acute serum, and the absence of anti-EBNA in both his sera make simultaneous primary infection with HHV6 and Epstein-Barr virus the most likely explanation of his serological findings. It is not possible to distinguish between the different scenarios in case 4 on the evidence available. Primary Epstein-Barr virus infection in childhood is usually accompanied by asymptomatic seroconversion, and postnatal primary cytomegalovirus infection is rarely a severe illness. It is tempting to speculate that the combined effects of infection with either of these viruses plus HHV6 are the cause of the considerable morbidity suffered by these two patients. There have been other reports of unusually severe illnesses due to double virus infections recently.[23 24]

The remaining four infants presented with illnesses entirely compatible with roseola infantum, although none was diagnosed clinically as such. The primary indication for serological testing in cases 5 and 6 was maternal pregnancy. A rapid diagnosis of acute HHV6 infection, by the demonstration of IgM anti-HHV6 in an acute serum sample, provides considerable reassurance in cases such as these. Cases 7 and 8 illustrate a further practical advantage in encouraging the accurate diagnosis of roseola, namely the avoidance of inappropriate prescribing of antibiotics in a febrile child.[14] Furthermore, if the diagnosis is roseola, the child may be wrongly labelled as allergic to the drug.

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HIV-1 infection in a cohort of haemophilic patients

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Abstract

The course of HIV infection in 53 haemophilic patients aged 5–20 years was evaluated by clinical examination and laboratory tests. During the evaluation time (median 30 months) two patients died of AIDS and 32 patients (60%) deteriorated when assessed by the Brodt-Helm classification. Nineteen patients (37%) had decreased absolute helper cell counts (<500 CD4 positive cells/μl), and 45 patients (87%) had reduced helper cell to lymphocyte ratios (<0·35). HIV-1 was isolated from peripheral lymphocytes in 29 of 46 patients. As the disease progressed the number of positive viral cultures increased. Considerable progression of the HIV infection was seen in haemophilic children and adolescents during the median evaluation period of 30 months. The transition from symptomless HIV infection to immunodeficiency was easily recognised.

A lowered ratio of helper cells to lymphocytes seems to be a useful marker of the beginning of the deterioration of the immune system.

During recent years the rate of HIV infection in children has increased.[1–4] In addition to children of HIV infected mothers, and adolescents infected as a result of sexual intercourse or abuse of intravenous drugs, those with haemophilia were at risk as a result of treatment with clotting factor concentrates that had not been treated to inactivate viruses.[5] Depending on the child's age, HIV affects different stages of the developing immune system.[6] At the time of diagnosis the clinical features vary from a symptom free state to severe immunodeficiency.[7] AIDS has a poor prognosis in children and adults of all risk groups,[7] [8] but there is controversy about the prognosis of HIV infection in haemophilic patients compared with other groups at risk (P Becker, *et al.* Abstract presented at the IV International Conference on AIDS, Stockholm 1988; JK Stehr-Green, *et al.* Abstract presented at the IV International Conference on AIDS, Stockholm, 1988).[9–11]

There are few European studies dealing with the course of HIV infection in haemophiliacs and even less about children and adolescents.[12–14] In this paper we describe the course of HIV infection in 53 haemophilic children and adolescents.

Patients and methods

Of 155 haemophilic patients under 20 years of age who had been receiving commercial clotting factor concentrates for more than four years at the Institute for Experimental Haematology, 62 patients were seropositive for HIV infection in 1984 and 1985. Starting in March 1987, 53 of these 62 haemophilic children and adolescents aged 5–20 years (median 15 years) who were infected with HIV were followed up for 24–36 months (median 30 months). The boys were examined three to six times a year. Forty eight patients had haemophilia A and five patients had haemophilia B; in all cases the haemophilia was classified as severe (factor VIII or IX <1%). Informed consent was obtained from the patients or their parents.

The following diagnostic procedures were carried out at three to six month intervals for each patient: clinical and neurological examination and laboratory tests including red cell count, white cell count, measurement of the erythrocyte sedimentation rate (mm in the first hour), liver function tests, and measurement of peripheral lymphocyte subpopulations by flow cytometry with commercial monoclonal antibody reagents (obtained from Ortho Diagnostics or Becton Dickinson Monoclonal Center). In the case of illness (diarrhoea, oral thrush, or rash) microbiological studies of throat and stool cultures for infectious agents, urine cultures for cytomegalovirus, and cultures of cutaneous lesions for herpesviruses were done. Antibody to HIV was measured using a commercial enzyme immunoassay (Recombinant HIV 1 EIA, Abbott). HIV was cultured from peripheral blood mononuclear cells as described elsewhere.[15] As the Brodt-Helm classification does not take account of the patient's age,[16] it was used for analysis of progression (table 1). In addition this classification directs more attention to the helper cell count than the Centers for Disease Control (CDC) classifications.

During the study some patients received antibiotics and intravenous immunoglobulins. Zidovudine was given in three cases, thus fulfilling the CDC case definition of AIDS or being classified as CDC stage IV A.

Table 1 Brodt-Helm classification of HIV infection[16]

Stage	*Definition*
1a	Healthy, seronegative subject at risk of HIV infection
1b	Healthy, seropositive subject
2a	Seropositive patients with lymphadenopathy syndrome and a CD4:CD8 ratio between 0·5 and 1·0
2b	Seropositive patients with severe immunodeficiency and a $CD4^+$ T cell count of <350/μl
3	AIDS (CDC definition)

Table 2 Staging of HIV infection in 53 haemophilic children and adolescents at end of survey (15 December 1989)

CDC classification for patients aged <13 years (n=10)		*CDC classification for patients aged ≥13 years (n=43)*		*Brodt-Helm classification (n=53)*	
Stage	*No (No of deaths)*	*Stage*	*No (No of deaths)*	*Stage*	*No (No of deaths)*
P1B	1 (0)	IIA	4 (0)	1b	5 (0)
P2A	9 (1)	IIB	1 (0)	2a	29 (0)
		IIIA	21 (0)	2b	15 (0)
		IIIB	11 (0)	3	4 (2)
		IVA	1 (0)		
		IVC$_1$	2 (0)		
		IVC$_2$	2 (0)		
		IVB	1 (1)		

Results

STAGING

The actual staging of the patients by the Brodt-Helm method, and the CDC paediatric (<13 years old), and the CDC adult (13 years old or more) classifications is shown in table 2. Two patients had died by the time of writing, one of an HIV associated wasting syndrome and another of a progressive multifocal leucoencephalopathy.

By December 1989, nine of the remaining patients were less than 13 years of age and 42 patients were between 13 and 20; the different CDC classifications were used according to age. Four of the five patients with haemophilia B were classified as stage 2a, and one patient as stage 1b (Brodt-Helm).[16]

EVALUATION OF PROGRESSION

During the period of evaluation 32 patients (60%) deteriorated according to the Brodt-Helm classification, and two patients died of AIDS. The staging at the time of the first examination and after a mean observation time of 30 months is shown in table 3.

CLINICAL SYMPTOMS

Table 4 shows the infections and other disorders that developed during the evaluation time. Four patients developed AIDS.

Table 3 Progression of disease during median evaluation period of 30 months by Brodt-Helm classification in 53 haemophilic patients with HIV infection

Stage at first examination		*Stage at last examination*				*No who died*
		1b	*2a*	*2b*	*3*	
1b	29	5	15	8	1	0
2a	21	0	14	6	1	0
2b	2	0	0	1	1	1
3	1	0	0	0	1	1

Table 4 Symptoms in 53 haemophilic patients with HIV infection

	No of patients
Recurrent infections (more than three infections in six months, including otitis, sinusitis, and bronchopulmonary infection)	8
Herpes zoster	8
Oral candidiasis (not associated with antibiotic treatment)	4
Bilateral tumour of the parotid gland	3
Pneumonia	2
HIV associated wasting syndrome*	1
Progressive multifocal leucoencephalopathy*	1
Toxoplasmosis chorioretinitis*	1
Pneumocystis carinii pneumonia*	1
Fever of unknown origin	1
Impetigo	1

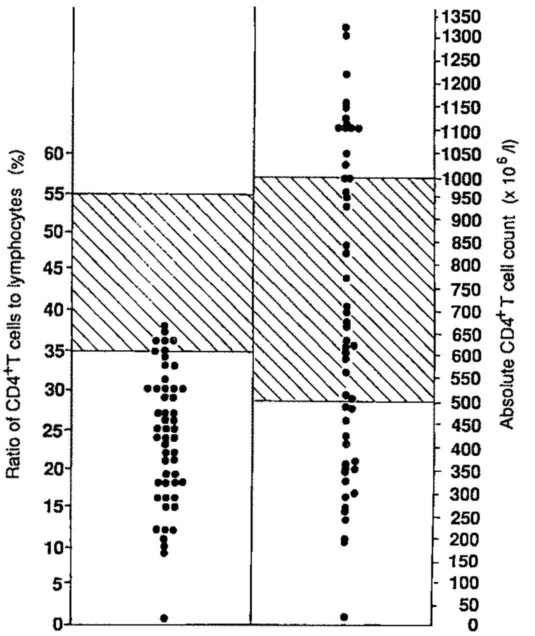
*Diagnoses fulfilling CDC criteria for AIDS.

LABORATORY TESTS

The figure shows a comparison between the absolute count of CD4$^+$ T cells and the percentage ratio of CD4$^+$ T cells to total lymphocytes after a mean observation time of 18 months. Nineteen patients (37%) had decreased absolute counts of helper cells (<500 CD4$^+$ T cells), whereas 45 patients (87%) already had a lowered ratio of helper cells to lymphocytes (<0·35).

VIRUS CULTURE

In 46 patients blood samples were available in which we attempted to culture HIV from



Distribution of the ratio of CD4$^+$ T cells:total lymphocytes (n=52), and absolute CD4$^+$ T cell count (n=52) in haemophilic children and adolescents infected with HIV. The hatched area indicates the reference range.

Table 5 Positive HIV cultures of lymphocytes from peripheral blood correlated with Brodt-Helm staging in 46 haemophilic patients

Brodt-Helm stage	*No of patients tested*	*No of cultures positive for HIV*
1b	2	0
2a	31	18
2b	11	9
3	2	2
Total	46	29

peripheral blood mononuclear cells. In 12 patients the first cultures for HIV were negative, but HIV was detected in a subsequent test several months later. In 17 patients the first virus culture was positive, so HIV could be cultured in the mononuclear cells of a total of 29 of the 46 patients (63%). If the virus culture was positive, repeated tests were also positive. The staging at the time of the first positive virus culture in these patients is shown in table 5.

Discussion

EVALUATION OF STAGING AND PROGRESS

The mean latent period before the development of AIDS is many years.[17] Primary infection with HIV in the patients in this study probably occurred between 1980 and 1983, before clotting factor concentrates that had been treated to inactivate viruses were introduced in 1984; their seroconversion was detected in 1984 and 1985. Most of the patients should therefore be in the latent state. This is confirmed by the actual staging six to 10 years after the probable date of primary infection (table 2). There are three patients in this study whose treatment was changed in 1981 to clotting factor concentrates that had been treated to inactivate viruses because of severe liver damage, so their HIV was probably inoculated before 1981. This might mean that these patients had HIV infection but had not developed AIDS for more than nine years. Haemophilic patients have, however, died of AIDS three years after inoculation of HIV (N Wagner, *et al.* Abstract presented at the IV Interational Conference on AIDS, Stockholm 1988). There is controversy about the course of HIV infection in haemophilic patients, particularly about the incubation period of AIDS or HIV related symptoms (P Becker, *et al.* Abstract presented at the IV International Conference on AIDS, Stockholm 1988; JK Stehr-Green, *et al.* Abstract presented at the IV International Conference on AIDS, Stockholm 1988).[9–11 18] In this study progression of the disease has been shown during an observation time of 30 months, and it is comparable with the development of HIV infections in other risk groups (GW Rutherford, *et al.* Abstract presented at IV International Conference on AIDS, Stockholm 1988).[16] In addition, immunological tests were abnormal in a larger number of patients with HIV after 18 months evaluation (figure) compared with haemophiliacs not infected with HIV (E Berntorp, *et al.* Abstract presented at XVIII International Congress of the World Federation of Haemophilia, Madrid 1988).[19] These results might be early signs of immune deterioration. No difference in staging of HIV infection between the patients with haemophilia A and the few with haemophilia B could be detected.

Recently Goedert *et al* reported a prospective study of the development of AIDS in a large cohort of haemophiliacs infected with HIV. Their findings showed that there was an age related risk for AIDS with a lower risk in the younger group (the incidence rate of AIDS after seroconversion was 0·83/100 patient years in those who were 1 to 11 years old compared with 5·66 in those aged 35 to 70 years).[20]

The results of our study show a remarkable progression of HIV infection in haemophilic children and adolescents during a median period of 30 months, especially the transition from symptomless infection to lymphadenopathy syndrome, and to pronounced immunodeficiency with a $CD4^+$ cell count of <350/μl. Whether there is a significant difference in the rate of progression compared with other risk groups (adult haemophiliacs, homosexual men, and drug addicts) cannot be concluded from these data. There is no doubt, however, that infants infected with HIV prenatally or perinatally often show progression of HIV related disease during the first year of life.[21–23]

CLINICAL SYMPTOMS

Even before the development of AIDS, HIV infection is associated with a number of symptoms. In this study mild infectious diseases were often diagnosed. These findings are consistent with other studies, which also show the range of the early stages of a paediatric HIV infection.[24–26] A remarkable number of cases with herpes zoster was found. This could be of clinical importance, as infections with herpesviruses may act as cofactors in HIV infection.[27]

LABORATORY TESTS

The absolute number of helper cells is of clinical importance, as there will be a high risk of opportunistic infections if the $CD4^+$ T cell count is below 150/μl.[28] The ratio of helper cells to total lymphocytes (this is not the CD4:CD8 ratio but the CD4:total lymphocyte ratio) has been shown to be a prognostic indicator (JV Giorgi, *et al.* Abstract presented on the IV International Conference on AIDS, Stockholm 1988).[10] The predictive value of the absolute count of helper cells is limited, as both the total and the differential white cell count and flow cytometry are necessary for calculating the absolute number of $CD4^+$ cells. The total and differential white cell counts, however, vary with non-specific infections. As a consequence, the absolute helper cell count does not seem to be useful as an early predictive sign of an initial deterioration of the immune system in HIV infection.

In our experience, however, the ratio of helper cells to lymphocytes varies less than the absolute helper cell count, confirming the work of other authors.[29] Moreover, in the patients of this study subnormal $CD4^+$ T cell to lymphocyte ratios were seen earlier in HIV infection than those of the absolute $CD4^+$ T cell count (figure). Altogether 37% of the patients showed an absolute helper cell count of less than 500 cells/μl, whereas 87% of the patients had a decreased ratio of CD4 cell:lymphocytes of less than 0·35 after a median evaluation period of 18 months. This is, of course, partly a result of the reactive increase in $CD8^+$ T cells. A ratio of less than 0·25 may, however, be a negative prognostic sign for patients who still have absolute helper cell counts within the normal range. This hypothesis will be studied by evaluation of progression in the future.

Another important indicator of progression of HIV infection is the results of virus cultures.[30] Despite the low number of positive virus cultures reported here, the rate seems to increase as the disease progresses. This is in accordance with the results of other investigations.[31]

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Archives of Disease in Childhood 1990; 65: 1305–1307

Rectal temperature of normal babies the night after first diphtheria, pertussis, and tetanus immunisation

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Abstract

Continuous rectal temperature recordings were made from 32 babies the night after their first diphtheria, pertussis, and tetanus immunisation and compared with recordings made before immunisation. Tog values of clothes and wrapping and room temperatures were also recorded. We found that immunisation the day before disturbs the normal night time rhythm of deep body temperature. The rectal temperature of immunised babies was significantly higher than non-immunised babies from two hours into the night. We also found that there were considerable individual variations in the extent of disturbance of temperature rhythm. They were not correlated with thermal environment. There is no reason to suppose that these mild physiological responses to immunisation are in any way harmful.

Babies aged 3–4 months exhibit a characteristic pattern of rectal temperature change during a night's sleep,[1] which is maintained across a very wide range of parental practice of room heating, clothing, and wrapping,[2] indicating a considerable capacity for thermoregulation. Although this rhythm is very resistant to disturbance by changes in thermal environment, it may be affected by changes within the baby, such as a developing infection, and it has been suggested that under these conditions a warm environment may be less tolerable.[3]

Nearly all babies receive their first diphtheria, pertussis, and tetanus (DPT) immunisation at about this age, which provides an opportunity to study the effects on body temperature of a standardised dose of an infective agent administered at a known time to babies who will subsequently sleep under a wide range of different thermal conditions. While it is known that some babies show a small rise of body temperature the night after immunisation,[4] there are no reports of continuous records of body temperature, or the effects of different thermal environments on the response. In this paper we report on the changes in rectal temperature of babies sleeping at home the night after their first DPT immunisation, and relate changes in body temperature to thermal environment.

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Methods

A random sample of 31 babies due for their first DPT immunisation was recruited by liaison with general practitioners in Leicester. They were visited on a night before immunisation, and basic perinatal data recorded, together with naked body weight, skinfold thickness, and head circumference. Thermistor probes were then attached to the babies, and rectal temperature (soft probe 5 cm from the anal margin), skin temperature on the abdomen (2 cm left of the umbilicus), and skin temperature on the forehead were recorded. A fourth probe measured room temperature by the cot side. All probes were connected to a Grant Squirrell data logger set to record once a minute throughout the night. These recording techniques have all be validated, and shown to be safe.[1] Full ethical committee approval was obtained for the study.

Note was made of each item of clothing and wrapping used by parents and a tog value calculated according to formulas supplied by the Shirley Institute, Manchester. The parents were also asked to maintain a diary of the night's events, including feeds, and times at which they were disturbed by the baby.

The recording was repeated the night after immunisation and the family contacted one week later to check on the health of the baby.

The data from the logger were read into a computer and scrutinised for evidence of technical problems, such as loss of probes. Only unblemished data were analysed. In this paper we report on the rectal temperatures. For each night of successful recording, rectal temperature was abstracted at 30 minute intervals from one hour before bedtime till nine hours later. Data at each time point from different babies before and after immunisation were analysed to yield mean rectal temperature and its standard error.

Results

Of the 31 subjects studied 17 were boys and 14 girls. The average (SEM) age at immunisation was 15·03 (0·79) weeks. Only four babies were older than 16 weeks. Eight of the babies were immunised between 09·00 and 10·00, the remainder between 14·00 and 16·00. The mean maternal age was 28·56 (1·06), and the social class distribution resembled that of the general Leicester population. All but one of the babies slept in their own cots, mostly in a separate room. The recordings were made during spring and summer 1989, and the maximum room temperature at night averaged 21·97 (0·98)°C before and 23·24 (0·68)°C after immunisation. The minimum room temperature was 18·95 (0·78)°C before and 19·47 (0·42)°C after immunisation. Babies were clothed and wrapped with 10·36 (0·91) tog units (range

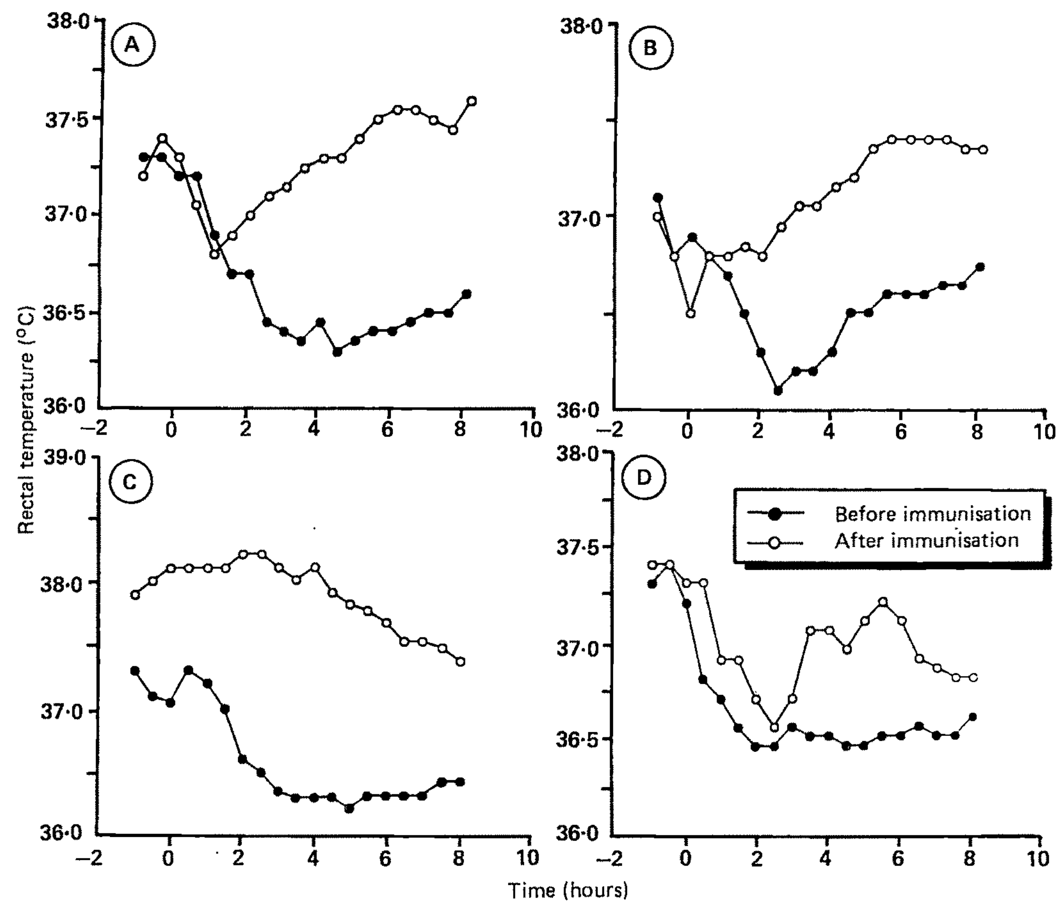

Figure 1 The rectal temperatures of four babies during the night before and after the first DPT immunisation.

4·6–15·9) before and 9·48 (0·63) units (range 3·2–17·0) after immunisation. There were no significant differences in thermal environment between recordings before and after immunisation.

Figure 1 shows typical individual records of rectal temperature over the nights before and after immunisation. The most common pattern of temperature change after immunisation is that shown in 1A and 1B. Before bedtime the rectal temperature is the same as a normal night, and after bedtime the temperature begins to fall, but after an hour or two it rises again to levels well above those before immunisation. One baby had a raised rectal temperature at bedtime, which was maintained throughout the night (fig 1C). Six babies showed no differences between temperature patterns before and after immunisation.

Figure 2 shows figures averaged before and after immunisation. The curve before immunisation is indistinguishable from those that we have reported earlier in normal infants, but after immunisation rectal temperature was significantly higher than before from two hours after bedtime until seven hours later.

At bedtime the rectal temperature before immunisation was 37·18 (0·03)°C and after 37·18 (0·08)°C. Four hours later it was 36·43 (0·07)°C before and 36·93 (0·09)°C after

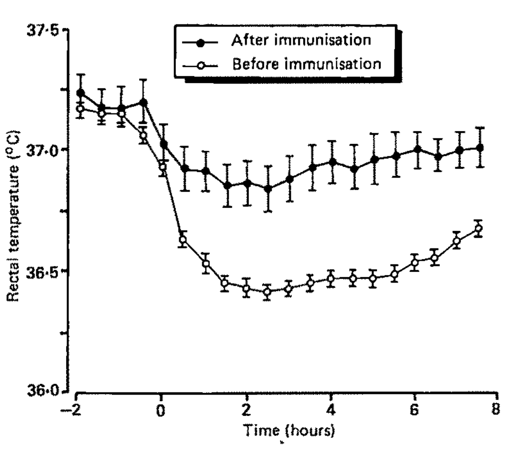

Figure 2 The mean rectal temperature of babies during the night after the first DPT immunisation compared with that during the night before immunisation. Bars show SEM.

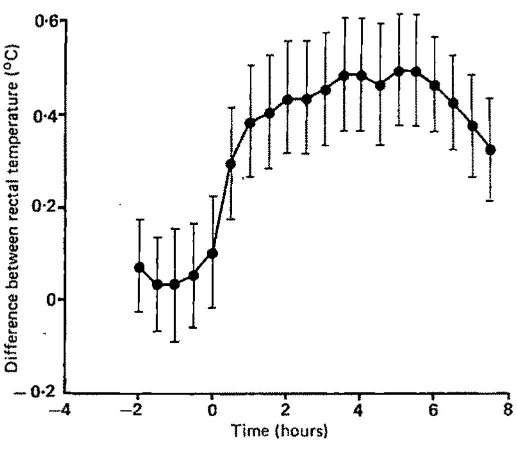

Figure 3 The differences between babies' rectal temperatures at various times during the night before and after first DPT immunisation. Bars show SEM.

immunisation. The differences between the means before and after were significant ($p<0{\cdot}01$ at least by *t* test) from two hours after bedtime (fig 3). The median rectal temperature four hours after bedtime was 36·78°C after immunisation. Those babies above median rectal temperature were not in significantly warmer rooms, nor were they significantly more insulated by clothing and wrapping. The babies whose temperature exceeded 37·3°C were also not in warmer rooms, or more insulated than the rest. Those above median rectal temperature were, however, of significantly lower birth weight ($p<0{\cdot}02$, Student's *t* test with 29 df) and tended to come from social classes IV and V. There was no difference in temperature pattern between babies immunised in the morning or afternoon.

Some of the babies were reported by their parents to have a 'disturbed night' after immunisation, but, on average, the babies did not disturb their parents more often the night after immunisation. Nor were they fed more often.

Five of the babies were given paracetamol (as either Calpol or Disprol) during the evening or night. The rectal temperature of the treated babies was not higher than the others either before or after the medication.

Discussion

Immunisation, a highly standardised infective challenge, leads to a disturbance of the normal night time rhythm of deep body temperature in most babies, though the extent of the change varies between individuals.

Rectal temperature was not significantly different in non-immunised and immunised babies in nearly all cases at bedtime but, after initially falling as expected, rose to waking levels or above within a few hours. By four hours into the night half the babies were over two standard deviations above the mean rectal temperature of non-immunised babies at that time. The disturbance of the normal temperature rhythm seems to be a response to the immunisation, occurring only during the first night irrespective of the time of immunisation the previous day. In the few cases where we have monitored temperature during second and subsequent nights, no changes in temperature have been observed, though this work is still in progress and will be reported later. It is likely that central thermal control is affected, perhaps by a combination of systemic 'infection' and a local inflammatory response at the injection site, though it should be noted that the immunised babies did not become febrile, and there is no reason to suppose that the physiological response to immunisation reported here is any way harmful. We have observed a similar pattern of temperature change in babies who were thought to be in the early stages of a minor infection.

This rise of temperature was not merely the consequence of a 'disturbed night'. Overall, the babies did not disturb their parents more often the night after immunisation than before, though the two whose rectal temperature was highest were disturbed. Furthermore, our previous work shows that a disturbed night per se does not normally alter the rhythm of body temperature.[5]

The individual differences in temperature change the first night do not seem to be explained by different thermal environments. Those who showed the largest disturbance of temperature rhythm were not more heavily wrapped or in warmer rooms, despite the fact that some very high room temperatures (up to 28°C) were recorded in a hot summer.

The babies whose temperature rise was above median were, however, of lower birth weight suggesting that some feature of the baby rather than the environment determines the extent of temperature rise. Maybe the thermal response to immunisation provides a means of assessing the way babies will respond to other infective challenges.

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Factors influencing the body temperature of 3–4 month old infants at home during the day

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Abstract

Continuous recordings of rectal temperature were made from 40 normal infants, aged 3–4 months, at home during two days of normal activities. We found that the rectal temperature of a normal, healthy baby may vary from 36·0°C at night to 37·8°C during active periods of the day. During daytime sleep rectal temperature fell, but to a lesser extent, and for less time than during night time sleeps. Feeds raised the temperature unless the baby slept, when they reduced the rate of fall of temperature. Bottle feeds affected temperature more quickly than breast feeds. The changes in temperature during sleep and after feeds were independent of the room temperature or thermal insulation of clothing and wrapping.

During a normal night's sleep, the rectal temperature of 3–4 month old infants changes in a characteristic way,[1] irrespective of ambient temperature or the thermal insulation of clothing and wrapping within the range normally chosen by parents.[2] This shows that by this age the adult circadian rhythm of body temperature is beginning to appear,[3] though the timing of temperature change is not precisely locked to time of day, rather to time of going to sleep.

It may be therefore, that the fall in rectal temperature at night is merely a consequence of sleeping, and not a true circadian rhythm. Babies of this age, however, also sleep during the day, so we can test this hypothesis by monitoring temperature during daytime sleeps, the longest of which can be similar in duration to short night time sleeps. Babies are also fed at bedtime, but not always before day time sleeps, so we may also be able to examine the effects of feeds on the rectal temperature in sleeping and awake babies. In this study therefore we have measured rectal temperature during daytime sleeps, and examined the interactions between the effects of feeding and sleeping on rectal temperature during the day.

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Methods

Forty normal full term babies were recruited at birth, and arrangements made to visit them at home on at least four occasions around 3 months of age. At the first visit basic perinatal data were recorded, together with body weight, head circumference, and skinfold thickness. On each visit three thermistor probes were attached to the baby (a soft rectal probe inserted 5 cm from the anal margin, and skin probes placed on the forehead and abdomen), and connected to a Grant Squirrell data logger set to record temperatures once a minute. Parents could, if they wished, interrogate the logger, but temperatures were not routinely displayed to them. A fourth probe measured room temperature. We have validated these recording techniques, and shown them to be safe.[1] Full ethical committee permission was obtained for this study.

Two recording periods were during the day, and two overnight. The data reported here are from the daytime recordings only except that some data from night time sleeps have been included for purposes of comparison. These recordings, of four to seven hours' duration, were chosen to span a normal range of daily activities. Parents were asked to keep a detailed, prospective diary of all the day's events, including feeds, sleeps, nappy changes, periods of activity, etc. In the case of daytime sleeps, parents were asked to check whether the baby was still asleep at 10 minute intervals, so that a reasonably accurate estimate of sleep duration could be obtained, though of course this disturbance may have led some babies to wake a little earlier than normal. At each recording note was made of the number of items of clothing worn by the baby, and the wrappings placed around it for periods of sleep. Tog values were calculated by reference to a table of figures provided by the Shirley Institute, Manchester.

The temperature data were read into a computer, and scrutinised for technical problems, such as loss of probes. Only unblemished data were analysed.

The temperature records were collated with the parental diaries, and periods of recording before and after feeds, or the onset of a sleep identified. In this paper we report on the rectal temperatures. Rectal temperatures were collated at 10 (feeds) or 15 (sleep) minute intervals, and mean and standard errors calculated at each time point. Statistical comparisons were by paired t tests between values at different times for the same individuals, where appropriate, and by unpaired t tests between groups if no pairing was possible.

Results

Of the 40 subjects studied 22 were boys and 18 girls. The mean (SEM) age at recording was 16·5 (0·39) weeks. The mean maternal age was 26·95 (0·92), and the social class distribution resembled that of the general Leicester population. When awake and active the babies were clothed with an average of 4·83 (0·17) tog units of insulation (range 3·2–6·2), in rooms whose temperatures averaged 18·11 (0·40)°C (range 10·8–21·7). During sleep they were wrapped with an additional 8·56 (0·42) tog units of insulation (range 6·9–20·1), in rooms whose ambient temperature averaged 17·64 (0·41)°C (range 8·7–21·3).

To measure the effects of sleep 76 daytime sleeps were recorded, of average duration 87 (17) minutes. Of these 31 were preceded by a feed, and the remainder followed a period (>1 hour) of activity, but were not preceded by a feed.

Figure 1 shows rectal temperature during the 31 sleeps which lasted at least 90 minutes. Temperature fell significantly by 45 minutes into the sleep, with a faster rate of fall in babies who were not fed. For both fed and non-fed babies during the day, rectal temperature 45 minutes after bedtime was significantly lower than at bedtime ($p<0·01$ paired *t* test with 11 and 18 df respectively): fed babies 37·21 (0·05)°C at bedtime and 36·82 (0·07)°C 45 minutes later ($n=12$). For non-fed babies it was 37·03 (0·06)°C at bedtime and 36·70 (0·04)°C 45 minutes later.

At 15 and 30 minutes after bedtime, rectal temperature was also significantly lower in non-fed babies than in fed babies: at 15 minutes in fed babies 37·04 (0·05)°C and in non-fed 36·79 (0·05)°C ($p<0·01$ unpaired *t* test with 29 df). At 30 minutes in fed babies it was 36·87 (0·06)°C and in non-fed 36·71 (0·04)°C ($p<0·05$ unpaired *t* test with 29 df). It rose again before waking. Figure 1 also shows rectal temperature during the first hours of a night's sleep for comparison. The initial rate of fall at night is like that of fed babies during the day, but it continues for longer at night, to stabilise at a significantly lower value. All babies were fed before their night time sleeps. These data were derived from measurements on the subjects from this study, though they are very similar to our previous reports from recordings of another group of babies.[1]

Neither the rate, nor the extent of temperature fall was affected by room temperature or tog value of clothing and wrapping. It was not uncommon for babies well wrapped in warm rooms to cool more quickly, and to a greater extent than those lightly wrapped in cool rooms.

Rectal temperature also falls during short (<1 hour) daytime sleeps, though the fall is transient, as rectal temperature has normally returned to above 37°C by the time of waking.

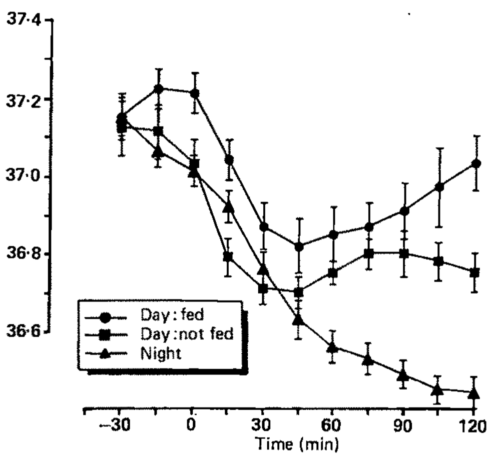

Figure 1 The mean (SEM) rectal temperature of 3–4 month old babies during daytime and night time sleeps.

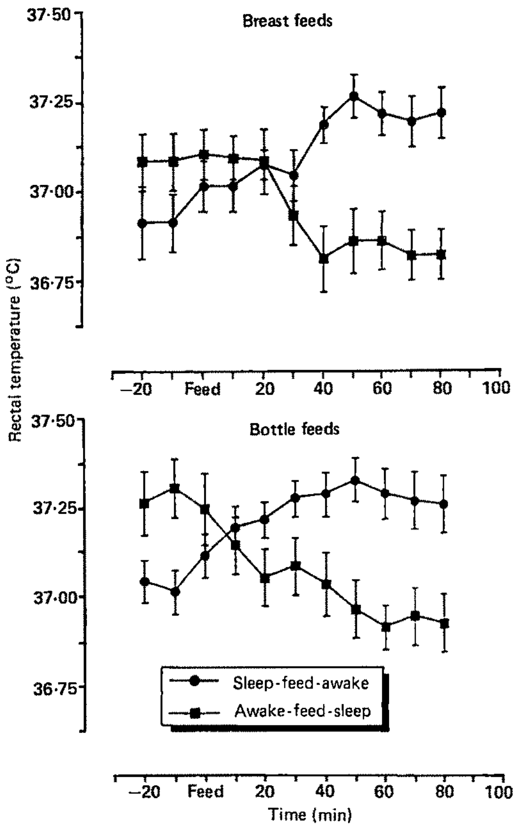

Figure 2 The mean (SEM) rectal temperature of 3–4 month old babies after breast feeds and bottle feeds, followed by either a period of waking or sleep during the day.

Sixteen of the subjects were wholly breast fed, 22 bottle fed, and two fed at breast and bottle. Most were also given some solids, with bottle fed babies generally given more. Reliable temperature records were obtained before and after 37 bottle feeds and 27 breast feeds. The majority of daytime feeds were followed by a period of waking (27/37 bottle feeds, 15/27 breast feeds), the remainder by sleep within 30 minutes.

Figure 2 shows rectal temperature changes after breast and bottle feeds during the day followed either by sleep or waking. Most feeds followed by waking were preceded by sleep, and vice versa. Rectal temperature 50 minutes after the feed was significantly raised if the baby remained awake, but significantly reduced if it slept: for bottle fed at feed time 37·11 (0·06)°C and 50 minutes later 37·32 (0·06)°C, $p<0·05$ by paired *t* test, 26 df; for breast fed at feed time 37·01 (0·07)°C and 50 minutes later 37·26 (0·05)°C, $p<0·05$ by paired *t* test, 14 df. For bottle fed babies at feed time who then slept the rectal temperature was 37·24 (0·08)°C and 50 minutes later 36·96 (0·08)°C, $p<0·05$ by paired *t* test with 9 df; for breast fed babies at feed time who then slept 37·10 (0·07)°C and 50 minutes later 36·86 (0·09)°C, $p<0·05$ by paired *t* test, 11 df. The rectal temperature of bottle fed babies rose faster if they stayed awake, and fell more slowly if they slept.

As with changes after sleep we could find no significant effects of room temperature, or tog value of clothing and wrapping upon the temperature changes after feeds.

Discussion

The rectal temperature of a normal 3 month old baby may vary from a minimum of 36·0°C during the night to 37·8°C during active periods of the day.[1] These variations are not, however, random. Temperature is affected in predictable ways by sleep, feeding, activity, and time of day per se.

Sleep at any time leads to a fall in rectal temperature, but there is an interaction between sleep and time of day. At night temperature falls by 0·8°C within two hours of bedtime, and remains low for several hours, even if the baby wakes for a while,[4] a pattern like that of adults.[3] During daytime sleeps temperature also falls, often at a faster rate and particularly in babies who have not been fed. The extent of fall is not, however, so great even in sleeps of similar duration. Even when babies sleep for over three hours during the day, their rectal temperature is above 37°C well before they wake, whereas babies who wake after three or four hours at night show only a very transient rise in temperature.[4]

During both night and daytime sleeps the rate and extent of temperature fall is independent of both room temperature and thermal insulation of clothing and wrapping within the range chosen by parents, indicating a controlled change, presumably driven by changes in the central 'thermostat'. By 3 months of age, however, this control operates differently during the night and day presumably because of the emergence of circadian rhythms in various physiological systems.[3]

Feeds and activity both tend to raise rectal temperature. It is not uncommon for a recently fed, active baby to have a rectal temperature of 37·8°C. In our studies about 15% of recently fed, active babies maintain rectal temperature above 37·7°C for half an hour or more. The effects of feeds are presumably due to the specific dynamic action of the food. This leads to a rise in temperature if the baby is awake, but if asleep, then temperature still falls, albeit more slowly than if the baby has not been fed.

The effects of bottle feeds on temperature appear much more quickly than those of breast feeds. It is possible that the temperature of bottle milk is higher than the babies body temperature, so that it provides some direct heating, but it is also likely that the bottle fed babies take more milk more quickly. The bottle fed babies were also much more likely to be given some solid food, such as rusk or baby rice.

It is clear, however, that a temperature that may be perfectly normal under some conditions can be quite abnormal under others, and if a spot reading of deep body temperature in a baby is to be correctly interpreted, then the time of day, sleep state, and feeding history must be known.

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Abnormal small bowel permeability and duodenitis in recurrent abdominal pain

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Abstract

Thirty nine children with recurrent abdominal pain aged between 5·5 and 12 years, underwent endoscopic duodenal biopsy to find out if there were any duodenal inflammatory changes, and if there was a relationship between duodenal inflammation and intestinal permeability to ^{51}Cr-EDTA. Duodenal inflammation was graded by the duodenitis scale of Whitehead *et al* (grade 0, 1, 2, and 3). In 13 out of 39 patients (33%) definite signs of inflammation were found (grade 2 and 3). Intestinal permeability to ^{51}Cr-EDTA in patients with duodenitis (grade 1, 2, and 3) was significantly higher (4·42 (1·73)%) than in patients with normal (grade 0) duodenal biopsy appearances (3·3 (0·9)%). A significant association was found between duodenal inflammation and abnormal intestinal permeability. Our results give further evidence that there is an intestinal origin of these patients' complaints.

About 10–15% of children of school age regularly complain of abdominal pain.[1 2] In most cases no underlying cause can be found. In a large study done in 1958 Apley claimed to be able to find somatic causes, such as urinary tract infections and peptic ulcers, in only 10% of the patients.[2] Since then various other possible causes have been suggested, including lactose intolerance,[3] abnormal gastroduodenal motility,[4] and even 'appendiceal colic'.[5] Much attention has been drawn by psychosocial conditions as a potential cause of the complaints.[6 7] Case controlled studies, however, have not established a clear relationship between abdominal pain and psychosocial conditions.[8 9]

In a previous study we report abnormal intestinal permeability in children with recurrent abdominal pain, using orally administered ^{51}Cr-EDTA as a marker.[10] In 54% of our patients we found that the ^{51}Cr-EDTA excretion was more than 3·5%, considered to be the upper limit of the reference range in children.[11] As the urinary excretion of ^{51}Cr-EDTA has been shown to be abnormal in several conditions known to be associated with mucosal inflammation such as coeliac disease,[11] Crohn's disease,[12] and gastroenteritis,[13] we suggested that intestinal inflammation may be present in our patients with recurrent abdominal pain. We had no histological evidence to support this hypothesis, however. The purpose of the present study therefore was to find out the incidence of intestinal inflammation in our patients with recurrent abdominal pain and to assess the value of ^{51}Cr-EDTA permeability tests of intestinal inflammation. As the absorption of ^{51}Cr-EDTA takes place predominantly in the small bowel,[12] duodenal biopsies from 39 patients with recurrent abdominal pain were examined for the presence of inflammatory changes.

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Patients and methods

During a prospective study 106 children with recurrent abdominal pain were investigated according to a standard protocol. Patients were diagnosed as having recurrent abdominal pain if they were aged between 5·5 and 12 years; had had recurrent abdominal pain for at least six months; had had attacks of pain varying in severity, duration, and frequency; and if their attacks were sometimes accompanied by paleness, nausea, and vomiting. These criteria are in accordance with those first laid down by Apley,[1 2] except for the duration of the complaints, for which we felt that a six month period was more justifiable. All children referred to our outpatient clinics with recurrent abdominal pain and those admitted to the paediatric ward who met the inclusion criteria, were admitted to the study. All children were referred to us by their family doctors or by school doctors. Both groups of colleagues were informed about the study. All parents gave informed consent, in only two cases did the parents refuse to take part.

The protocol consisted of a standard physical examination; routine laboratory investigations of blood, faeces, and urine, and a standard ultrasound examination of the abdomen. Lactose tolerance was tested with an oral lactose load of 2 g/kg body weight, with a maximum of 50 g. Breath samples were analysed at 30 minute intervals for two hours, with a Lactoscreen (HoekLoos). Hydrogen content of breath samples was considered abnormal if it exceeded 20 ppm.

The ^{51}Cr-EDTA permeability test was done as previously described.[10] Briefly, after an overnight fast a dose of 100 μCu ^{51}Cr-EDTA was given orally in 10 ml of 5% glucose. Urine was collected for 24 hours. Urine volumes were measured and two samples of 5 ml each were counted in a well counter. A standard 1/100 dilution of 5 ml was similarly counted. Radioactivity excreted in the urine over a period of 24 hours was expressed as a percentage of the oral dose. In a previous paper, our control group of children showed a mean (2SD) ^{51}Cr-EDTA excretion of 2·5 (1·3)%.[13] We therefore chose a cut off value of 3·8% to evaluate the relationship

Table 1 Clinical features of children with recurrent abdominal pain

	Duodenal biopsy (n=39)	*No duodenal biopsy (n=67)*
Sex (male/female)	15/24	23/44*
Mean age at entry (years)	8·25	9·23*
Range	5·9–14	5·5–12·4
Mean duration of complaints (months)	26·8	19·4*
Range	6–120	6–80
Mean No of attacks/week	4	3·9*
Range	Once a month–every day	Once a month–every day
Mean duration of attacks (hours)	6·3	5·3*
Range	5 min–all day	5 min–all day

*No significant differences between groups (Wilcoxon test).

Table 4 Relationship between ^{51}Cr-EDTA test results and duodenal inflammatory changes

	^{51}Cr-EDTA excretion (%)		*Total*
	≤3·8%	*>3·8%*	
Grade 0	9	2	11
Grade 1, 2, 3	12	16	28
	21	18	39

Relationship between abnormal small bowel permeability and duodenal inflammation: p=0·03 (Fisher's test, single tailed).

between small bowel permeability and duodenal inflammatory changes.

Clinical details regarding our patients are shown in table 1. Of 106 patients with recurrent abdominal pain, 39 underwent endoscopy and biopsy of the duodenum. Duodenal biopsy specimens were taken after an overnight fast from the proximal duodenum with an Olympus GIF XP10 endoscope. All patients were sedated with midazolam (Dormicum) and atropine. One or two biopsy specimens from each patient were immediately placed in Bouin fixative. After embedding in paraffin they were cut into 4 μm sections and stained with a haematoxylin and eosin. The most representative, well orientated sections were used for grading. Histological grading of duodenal inflammation was done according to the criteria laid down by Whitehead *et al.*[14] The histological sections were examined by a pathologist who had no knowledge of the clinical or endoscopic findings. All sections were reviewed for this study by the same observer (JWA).

Although a certain bias may have been introduced in the group of patients (n=39) who underwent duodenal biopsy (37% of the total study group), there appeared to be no significant differences between the two groups in clinical data (table 1) or ^{51}Cr-EDTA excretion (table 2). There was, however, a tendency towards higher ^{51}Cr-EDTA excretion values and a slightly longer duration of complaints in the group that underwent biopsy.

Only the results concerning intestinal permeability and duodenal biopsy results are reported in the present paper.

Table 2 Urinary ^{51}Cr-EDTA excretion in different groups of patients

	All patients with recurrent abdominal pain (n=100)	*Duodenal biopsy (n=39)*	*No duodenal biopsy (n=61)*
^{51}Cr-EDTA excretion (%)	3·60*	4·11*	*3·24*
SEM	0·16	0·26	0·19
Range	1·1–10	1·9–10	1·1–8

*No significant differences between groups (*t* test).

Table 3 Results of the ^{51}Cr-EDTA permeability test in 39 patients with recurrent abdominal pain with varying degrees of duodenal inflammation

	Duodenitis				
	0 (n=11)	*1 (n=15)*	*2 (n=10)*	*3 (n=3)*	*1, 2, and 3 (n=28)*
^{51}Cr-EDTA excretion (%)	3·3	4·64*	4·34	3·67	4·42**
SEM	0·27	0·49	0·53	0·59	0·33
Range	1·9–4·7	2·4–10	2·3–7·5	2·3–4·8	2·3–10

Compared with grade 0: *p<0·002, **p<0·05 (*t* test).

Results

Of the 39 patients who underwent duodenal biopsy, 13 (33%) showed microscopically obvious signs of inflammation (10 and three with Whitehead grades 2 and 3, respectively), 15 (38%) showed minimal changes (grade 1), whereas in 11 patients (28%) the biopsy specimens looked normal (grade 0). A simultaneous antral biopsy was taken from 11 of these patients; in eight cases (73%) *Helicobacter pylori* colonisation was detected on histological examination (three with grade 0, one with grade 1, 2 with grade 2, and two with grade 3 duodenitis). Histological evidence of gastritis was present in four (50%) of the patients in whom *H pylori* was found. The combination of gastritis and duodenitis was present in three of the eight patients in whom *H pylori* was found. Results of 24 hours ^{51}Cr-EDTA excretion in all our 106 patients with recurrent abdominal pain are presented in table 2. In six cases either the parents refused the test or urine sampling failed. The mean ^{51}Cr-EDTA excretion values of patients with varying degrees of duodenal inflammation are shown in table 3. The ^{51}Cr-EDTA excretion of patients with grade 1 duodenal inflammation was significantly higher than that of patients with grade 0 ($p<0{\cdot}02$, Student's *t* test). Most notably, no differences were found between patients with grade 2 or grade 3 on the one hand, and grade 0 on the other. The mean ^{51}Cr-EDTA excretion of patients with normal findings (grade 0), however, was significantly lower than that of patients with grades 1, 2, and 3 taken together ($p<0{\cdot}05$, Student's *t* test).

Table 4 shows the relationship between normal and abnormal small bowel ^{51}Cr-EDTA excretion values and the histological grading of the duodenal biopsy. It illustrates the significant relationship between abnormal small bowel permeability and inflammatory changes in the duodenum ($p=0{\cdot}03$, Fisher's exact test).

Discussion

In a group of 66 children with recurrent abdominal pain, Ament and Christie found duodenitis in only two cases and duodenal ulcers in eight, but these diagnoses were made endoscopically and not confirmed histologically.[15] In a group of 62 children with recurrent abdominal pain, Black *et al* described only nine cases with signs of histologically confirmed duodenitis.[16] They used a histological grading system different from ours, however, which makes comparison between the studies difficult. In a retrospective study of 320 gastroduodenoscopies in children, Oderda *et al* reported only 32 cases with endoscopic signs of duodenal damage.[17] Abdominal pain was the most common symptom in 25 of these patients (78%), and the criteria of Whitehead *et al* for the histological diagnosis of duodenitis were met in only four. It is remarkable that three of these patients had recurrent abdominal pain. More recently, Glassman *et al*, using Whitehead's criteria, reported duodenitis in 47% of 95 children with epigastric pain.[18]

The criteria of Whitehead *et al* are generally accepted for classifying inflammatory lesions in the duodenum. Grade 0 describes a normal histological appearance. Grade 1 describes 'minimal change' duodenitis, and grades 2 and 3 are definitely abnormal, indicating the presence of duodenitis.[14] The clinical relevance of the classification is, however, questionable, as minimal changes and even overt inflammation have been reported in healthy adult volunteers.[19] Whether these observations are also applicable to children is brought into doubt by the data of Oderda *et al*.[17] In the present study, a third of the patients with recurrent abdominal pain had definite signs of duodenitis: grades 2 and 3. Given the above reservations this supports our hypothesis that children with recurrent abdominal pain have a high incidence of intestinal inflammation.

Our results also show a significant relationship between intestinal permeability to ^{51}Cr-EDTA and inflammatory changes. The minimal inflammatory changes described as grade 1 are often regarded as still within the reference range. In this context, it is remarkable that in our group of patients with grade 1 the ^{51}Cr-EDTA excretion test yielded significantly higher results than in patients with normal findings (grade 0). Separately, however, patients with grades 2 or 3 duodenitis showed no significant differences from patients with grade 0. This discrepancy may possibly be explained by the small numbers of patients in these two groups. This might shed new light on the relevance of grade 1 inflammatory changes and suggest that minimal inflammatory changes should be considered as abnormal being the precursor of full blown duodenitis. Alternatively it might represent an early healing stage before abnormal small bowel permeability had returned to normal. On the other hand, in those children in whom there was increased ^{51}Cr-EDTA excretion together with a normal histological appearance of the duodenum, we are possibly dealing with false negative findings, as multiple biopsy specimens (which were not considered justifiable in this study), would be required to exclude the possibility of patchy lesions in the small bowel.

When (for the above mentioned reasons), all patients with inflammatory changes (Whitehead grades 1, 2, and 3) are taken together, there appears to be a significant relationship between abnormal ^{51}Cr-EDTA excretion ($>3{\cdot}8\%$) and the presence of inflammatory changes in the duodenum of patients with recurrent abdominal pain (table 3). On the basis of these numbers the ^{51}Cr-EDTA test has a sensitivity of 57% and a specificity of 82% for the detection of duodenitis. Despite the apparently low sensitivity of the ^{51}Cr-EDTA test, it still gives a positive predictive value of 89%. Used in this way the ^{51}Cr-EDTA may be a valuable diagnostic tool in children with recurrent abdominal pain, in screening for possible intestinal inflammatory changes. We certainly use it in clinical practice to find out if we are dealing with a possibly organic cause of the abdominal complaints; this we believe is justified by our findings in the present study.

The cause of the inflammatory changes in our patients still remains unclear. Recent studies (presented in a poster session at the first meeting of the European Campylobacter Study Group, Bordeaux, France, October 1988) by de Rafael *et al* and Mahony *et al* showed that *Campylobacter pylori* (now called *Helicobacter pylori*) was present in the antral mucosa of children with chronic gastritis and recurrent abdominal pain. *H pylori* has, however, an affinity for gastric mucosa.[20] Unfortunately, gastric biopsy specimens were not obtained from all patients in the present study. Glassman *et al* reported the presence of duodenitis without associated gastritis in 47% of patients from whom *H pylori* was not isolated, whereas duodenitis associated with gastritis was found in 56% of their patients from whom *H pylori* was isolated.[18] In our patients with grades 2 or 3 duodenitis and *H pylori* colonisation, three (37%) showed associated microscopic gastritis. Furthermore, small bowel permeability to ^{51}Cr-EDTA is abnormal in children with gastroenteritis,[13] a condition that is associated with duodenal mucosal inflammation.[21] Although we have only few data to support this contention, it seems likely that the inflammatory changes we found in our patients were in some cases caused by bacterial or viral infections.

Food hypersensitivity might also have a role in causing inflammation of the small bowel. Either a primary (food antigens) or a secondary (bacterial antigens) hypersensitivity reaction could result in a local intestinal inflammation whereby the intestinal wall could loose its ability to act as an effective barrier. The altered intestinal permeability would then allow the passage of more macromolecular antigens. This penetration of antigens could further aggravate the local hypersensitivity reaction, which would in the end result in widespread inflammatory changes and causes damage and disease.[22 23] Some authors found a correlation between the irritable bowel syndrome and hypersensitivity to food.[24–26] The symptomatology and pathophysiology in the irritable bowel syndrome seem closely related to recurrent abdominal pain in childhood.[27] The findings in our patients and data from other authors seem to support the hypothesis that food hypersensitivity might play a part in recurrent abdominal pain.

Further studies are needed to elucidate the pathophysiological mechanisms in recurrent abdominal pain. It seems likely, however, that small bowel inflammation whether primary or secondary to different environmental factors, may play an important part in the pathogenesis of this frequently misunderstood problem in childhood.

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Growth velocity before sudden infant death

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Abstract

Weight velocities of 136 infants who died from suddent infant death syndrome (SIDS) were compared with those of 136 controls matched for sex, birth weight, and type of feeding. It was found that the SIDS infants gained weight more slowly overall and that the differences were significantly different for infants who were not breast fed in the last two weeks in which it was possible to estimate their growth velocity. Breast fed infants had more periods of growth below the 25th centile than expected. These differences are unlikely to be useful in the prediction of which babies are likely to die from SIDS as there are frequent episodes of poor growth in infants who do not die.

A number of groups have addressed the issue of weight gain for infants who die from sudden infant death syndrome (SIDS).[1 2] Some have concluded that such infants gain weight slowly or show signs of delayed physical development.[3] Others believe, that while there may be some suggestion that SIDS infants grow more slowly than other children, the difference is so small and the normal individual variation so great that growth rate is unlikely to be useful as a predictor of SIDS.[2]

This study was part of a comprehensive case-control study which examined risk factors for SIDS in the South Island of New Zealand.[4] This area has a particularly high incidence of SIDS (6·3/1000 live births) compared with the rest of New Zealand (4·2/1000 live births) and the rest of the Western world (on average 2/1000 live births). In this part of the study the growth characteristics of a group of infants dying of SIDS are compared with infants matched for sex, birth weight, and type of feeding.

Patients and methods

The infants in the study were born in the Christchurch, Invercargill, and Dunedin Health Districts between January 1979 and December 1984. Information about the SIDS deaths was supplied by the National Health Statistics Centre, Wellington, and was cross checked with regional coroner's records. All necropsy and historical data were reviewed and the SIDS label given independently by two of the authors (EASN and BJT).[5] Of 377 infants who died of SIDS during that period, 297 (79%) attended clinics run by the Royal NZ Plunket Society. For the purposes of the risk factor study two controls were chosen for each infant.

For this part of the study the infants were chosen from those who attended Plunket Society clinics. As part of their surveillance service the Plunket nurses weigh children in their homes until they are 8 weeks old and in clinics until they are 5 years old. They also advise on feeding and management. To be included in this part of the study the infants had to have survived for at least four weeks, have a weight recorded within four weeks of death, have inter-weight intervals of less than six weeks in the first three months of life, and less than three months in the next nine months of life. Each infant was matched with an infant from the control group, who was of the same sex, had a similar birth weight, and had been fed in the same way. Infants were described as breast fed if they were mainly breast fed without supplements at the age of 4 weeks. All infants born at less than 37 weeks' gestation, twins, and those with a congenital anomaly likely to disturb growth were excluded. Because the weight data was essentially 'field data', the intervals between measurements were irregular. To overcome this problem a smoothing spline technique was used to derive regular two weekly weights.[6] This was done for as many infants as possible. Growth in terms of level, trend, and variability was compared between the two groups using paired *t* tests. The level of growth was defined as the average of the weights every two weeks up to the last one before death and was computed for each case. The same number of observations were used to compute a mean for the corresponding control. The second measurement was slope, trend, or average velocity and was calculated by method of least squares. Again, the death weight was excluded. This was measured in g/day. The square root of the residual variation was used as a measure of variation. This gives an indication of how closely the weight measurements fit the regression line (see figure).

We were also interested in the growth velocity within the last two complete two week periods before death of the SIDS infants and the corresponding period for their matched control. This was calculated by dividing the differences between successive spline measurement by 14, giving a velocity in g/day. The death weight of the SIDS infants, which was recorded by the pathologist at the time of the necropsy, was compared with the weight of the control infant for the equivalent day, calculated by linear interpolation.

Details of feeding and growth problems recognised by the Plunket nurses were extracted from the Plunket notes at the same time as the weight measurements.

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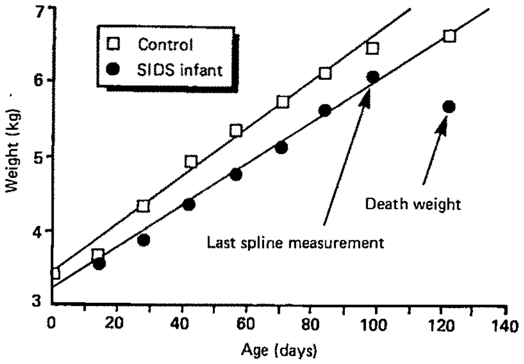

Example of pair of growth curves with regression line fitted. Death weight is shown for the case and estimated weight for the matched control at the same age.

The results are reported for breast fed infants and for those not breast fed separately because we had shown that growth rates for the first six months of life for the two groups were significantly different.

Of the 297 infants who had some contact with the Plunket Society, 33 were excluded because they were premature (gestational age 36 weeks or less) and 128 because their attendances at the clinic were too infrequent for reliable splines to be computed. Hence, this study was carried out on 136 infants (36% of the original sample and 46% of those seen by the Plunket Society). When the three groups were compared there were no significant differences for birth weight, length, and head circumference. There were, however, significant differences for mothers' age ($p<0{\cdot}01$). The mothers who did not take their babies to Plunket clinics were on average two years younger than those who did. The proportions of Maori and single mothers were similar.

Results

The figure shows the birth weights and the weights derived from the splines for a pair of infants. The last points are the death weight for the SIDS infant and the weight, obtained by linear interpolation, of the matched control on the same day. The slope of the line shows the average weight gain from birth to the last weight measurements derived from the splines.

The results for the breast fed infants whose mean age at death SIDS was 88·8 days (range 29–322) are reported in table 1. The difference for birth weights was significant, but it should be noted that the mean difference was only 4 g. The difference in weight at the time of death was also significant, the mean difference being 237 g. The differences between the SIDS infants and their controls for the last two spline measurements were not significantly different. The differences in overall growth velocity as well as those in the two periods between the last three spline measurements were not significantly different, though the SIDS infants grew on average at a slower rate than their matched controls throughout. The growth velocity between the last measurements and death differed appreciably. Some of this difference can be attributed to weight loss at the time of death. The variability of weight velocity did not differ between the groups.

Infants who had not been breast fed died of SIDS at a mean age of 77 days (range 31–157). the comparisons with the controls show a rather different pattern than those for breast fed infants and are shown in table 2. Like the breast fed infants they showed significant differences in weight at the time of death, the mean difference being 371 g. The difference in growth velocities was also more noticeable, with the difference in overall velocity approaching significance ($p<0{\cdot}07$) and a lower growth velocity for the two weeks between the last two spline measurements ($p<0{\cdot}01$). Again the difference between the last measurement and the weight at the time of death was significant. Variability of growth velocity was not different between groups.

In order to examine the difference in velocity gradients more closely, the results for the last two two week periods are reported in terms of

Table 1 Breast fed infants: means, standard deviations, and differences for weights and weight velocities

	No of infants	*Mean (SD)*	*Mean difference*	*t*	*p Value*
Weight (kg):					
Birth	88				
SIDS		3·43 (0·433)	0·00	−2·01	0·05
Controls		3·43 (0·432)			
Death	66				
SIDS		5·48 (1·330)	−0·24	−2·19	0·03
Controls		5·72 (1·335)			
Velocity (g/day):					
Birth to last spline measurement	88				
SIDS		25·5 (9·15)	−0·9	−0·62	0·54
Controls		26·4 (9·80)			
Last two weeks	46				
SIDS		26·3 (10·69)	−1·1	−0·50	0·62
Controls		27·4 (13·62)			
Penultimate two weeks	88				
SIDS		25·0 (11·31)	0·0	−0·01	1·00
Controls		25·0 (10·89)			
Last spline to death	66				
SIDS		18·4 (24·18)	−6·3	−2·60	0·03
Controls		24·7 (9·84)			
Variability (kg):	88				
SIDS		0·9 (0·73)	−0·2	−1·71	0·09
Controls		1·1 (0·97)			

Table 2 Non-breast fed infants: means, standard deviations, and differences for weights and weight velocities

	No of infants	*Mean (SD)*	*Mean difference*	*t*	*p Value*
Weight (kg):					
Birth	48				
SIDS		3·35 (0·630)	−0·01	−0·60	0·55
Controls		3·36 (0·550)			
Death	33				
SIDS		5·25 (0·859)	−0·37	−2·83	0·01
Controls		5·62 (0·910)			
Velocity (g/day):					
Birth to last spline measurement	48				
SIDS		28·4 (10·42)	−3·0	−1·86	0·07
Controls		31·4 (8·53)			
Last two weeks	21				
SIDS		25·6 (14·24)	−10·6	−3·15	0·00
Controls		36·5 (12·62)			
Penultimate two weeks	48				
SIDS		28·4 (11·34)	−3·1	−1·67	0·10
Controls		31·5 (12·59)			
Last spline to death	33				
SIDS		18·9 (22·93)	−12·8	−2·79	0·01
Controls		31·7 (14·58)			
Variability (kg):	48				
SIDS		1·1 (0·77)	−1·8	−1·22	0·23
Controls		0·9 (0·74)			

Table 3 Frequencies and percentages for growth velocities in the last two two week periods standardised for sex and age. Results are number (%)

	Penultimate two weeks		*Last two weeks*	
	SIDS	*Controls*	*SIDS*	*Controls*
		Breast fed infants		
Weight velocity quarters:				
First	34 (38·6)	22 (25·0)	19 (41·3)	12 (26·1)
Second	19 (21·5)	23 (26·1)	9 (19·6)	12 (26·1)
Third	16 (18·1)	25 (28·4)	6 (13·0)	11 (23·9)
Fourth	19 (21·5)	18 (20·5)	12 (26·1)	11 (23·9)
Total	88	88	46	46
		Non-breast fed infants		
Weight velocity quarters:				
First	12 (25·0)	6 (12·5)	7 (33·3)	2 (9·5)
Second	9 (18·8)	9 (18·8)	4 (19·0)	0
Third	14 (29·2)	16 (33·3)	5 (23·8)	8 (38·1)
Fourth	13 (27·1)	17 (35·4)	5 (23·8)	11 (52·4)
Total	48	48	21	21

quartiles standardised by age and sex. From table 3 it can be seen that in the last month of life around 40% of the breast fed SIDS infants had a least one two weekly growth velocity below the 25th centile. The number of controls was much closer to the expected 25%. This excess was not so noticeable among the non-breast fed infants. The percentage of SIDS infants below the 10th centile was also more than expected, 17% compared with 12% of the controls for the breast fed infants; the rates for the non-breast fed infants were similar.

Information was obtained from the Plunket clinic notes about weight gain. Among the breast fed infants the nurses noted poor weight gain in five (6%) SIDS infants and five (6%) controls during the first four weeks of life and in nine (10%) SIDS infants and seven (8%) controls between five and 12 weeks. Only one of the SIDS infants and one control among the non-breast fed infants showed poor weight gain in the first four weeks and five SIDS infants in the next eight weeks.

Discussion

The findings of this study are consistent with those of other studies, which showed that the weight gain of SIDS infants was less than that of normal infants.[1–3] This study suggests that the weight gain of breast fed infants who died of SIDS was not very different from that of infants who survived. There is some evidence, though, that in bottle fed infants the weight gain of the SIDS infants was considerably slower than the controls. The absolute level of weight gain of the SIDS infants was very similar to that of the breast fed infants, however, while the weight gain of the controls was greater. That fewer than expected non-breast fed control infants had growth velocities below the 25th centile is consistent with this finding as is the greater difference in death weight of bottle fed cases and controls compared with breast fed cases and controls. Despite there being more weight velocities below the 25th centile and the 10th centile, the number in the very low centiles was close to that expected, so it seems unlikely that the sort of weight velocity differences detected were clinically worthwhile.

It could be argued that fitting a linear trend to the data was inappropriate because weight gain, as can be seen from the figure, was not linear. But as we were interested in the differences in overall weight gain between each SIDS infant and his or her matched control, rather than differences in pattern of growth, comparing differences in slopes was a straight forward way of doing this. The similarity in variability in the two groups suggests that the growth patterns were not different though the variability overall may have been reduced by the smoothing spline technique.

One of the limitations of this study was that sufficient data to analyse growth adequately was available for only 136 of 377 infants who died of SIDS. It should be recognised, however, that all these infants were full term (37 or more weeks' gestation) and regular attenders at infant health clinics. The babies studied would therefore be generally a rather low risk group for SIDS. A prospective study with less 'drop out' may well find a higher incidence of growth failure. As our data was from routine health surveillance, we can say with some confidence that this degree of routine weight monitoring is unable to alter substantially the high incidence of SIDS in our community (7/1000 live births).

This study, like others, found a significant difference between the death weight of the SIDS infants and the weight of the controls. The differences in this study were not of the same magnitude as those reported by Peterson who suggested that they were as high as 500 to 1000 g.[7] He attributed some of the difference to agonal bowel and bladder evacuation and postmortem dehydration but did not adjust for differences in birth weight. Matching for birth weight was intended to overcome this problem as well as making the comparisons between growth velocities more meaningful. These results suggest that the difference in weight was around 240 g for the breast fed infants and 340 g for the others. The slower weight gain of the SIDS infants from the time of their birth as well as in the period just before their death is consistent with this, though it is difficult to know how much of the difference can be attributed to slow growth and how much weight loss after death.

Other studies, however, offer more support for the idea that infants are compromised by poor weight gain.[8] In examinations of thymus, rib, and liver in a series of 200 SIDS infants during necropsy it was found that more than 90% of them showed costochondral junction abnormalities. These were attributed to retardation in growth velocity and it was concluded that careful monitoring of these infants during life would have shown periods of slow growth in almost all. In another study in which apnoea monitors were compared with weighing scales in two groups of infants, who were siblings of SIDS infants, the weight fluctuations of 50 infants were described.[9] Their progress was plotted on special charts constructed in such a way that an infant was not expected to move up or down more than one channel width in a two week period or two channel widths in an eight week period. It was found that there were 17 falls in weight and that 16 of these were associated with illness. After the conclusion of the study one child, who had been in the apnoea monitor group, died of SIDS and it was found that his weight gain had been satisfactory until the 15th week but had remained virtually stable after that. It was suggested that his growth failure should have been detected before his death. On the basis of this study the authors have come to believe that daily weighing accompanied by weekly visits from the health visitor would be an acceptable way to monitor growth velocity and perhaps prevent SIDS. The less refined measurements obtained in this study suggest that many infants have experienced periods of slow growth, and that even though SIDS infants grow rather more slowly over long periods their gain in weight is in the main what is expected of infants at that stage of development. Thus monitoring their growth in this way is unlikely to identify potential SIDS victims. Monitoring their growth more closely may, despite the evidence of one study, lead to anxiety and is certainly more costly in terms of nurse time, but if it is thought to be worthwhile should be investigated in a large prospective study before being strongly recommended.

Our study suggests that weight monitoring would not appear to be useful in detecting babies likely to die of SIDS mainly because many infants who do not die of SIDS also have episodes of poor growth. Episodes of poor growth in our control group were often associated with the recording of symptoms that would explain the poor weight gain, however, and the detection of poor weight gain may lead to appropriate further investigation. The effectiveness of routine weekly weighing of babies with their further evaluation if the weight velocity falls below the 10th centile on two consecutive weekly periods needs to be evaluated in a large prospective study of infants at very high risk of SIDS.

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Increasing asthma prevalence in a rural New Zealand adolescent population: 1975–89

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Abstract

A survey of asthma symptoms and spirometry in 435 adolescent schoolchildren was undertaken in 1989 in a rural, largely Maori population. The survey questionnaires were identical to those used in a 1975 survey at the same school. The prevalence of reported asthma or wheeze significantly increased from 26·2% to 34·0%. This increase occurred in groups reporting asthma, and also those reporting wheeze unassociated with colds, but without a previous diagnosis of asthma. There was a tendency for a rise in reported wheeze in Europeans (24·3% to 27·4%) and a significant rise in Maoris (27·1% to 36·2%). The reclassification of other respiratory problems did not account for the increase. Data from this study provides evidence that there has been a rise in the prevalence of asthma in this New Zealand population over a time period of 14 years.

As New Zealand has had a higher mortality rate from asthma compared with other Western countries[1 2] there has been interest in the prevalence of asthma, and whether or not this is changing. A higher mortality rate from asthma at some ages among Maoris,[3 4] and the higher rate for hospital admissions among Maori children,[5 6] has also stimulated interest in the prevalence of asthma among this cultural group.

Most studies of asthma prevalence in this country have been undertaken in urban areas. One of the few studies in a rural area was by Stanhope *et al*, who undertook a large survey of adolescent health in Wairoa College third to fifth form students (age 12–18 years) in Hawkes Bay in 1975.[7] This included questions relating to asthma, wheeze, and respiratory health, a clinical chest examination, and baseline spirometry. According to census data the Wairoa area has changed little over the last 14 years in total population and in terms of the racial and socioeconomic structure. Wairoa College remains the only secondary school in the area taking students from both the rural farming district and the local towns. This, therefore, was an appropriate population in which to compare current asthma prevalence with that of 14 years ago.

From a survey of current Wairoa College students we report the prevalence of asthma symptoms in a rural New Zealand teenage population, of which a high proportion were of Maori origin. In addition we report the changes in prevalence of asthma symptoms in this population after 14 years.

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Methods

The current survey was performed over four weeks, during August and September 1989. Each participating student was given a questionnaire, which was completed at home with the help of a parent if necessary. A structured interview followed at school. The survey technique and format of the questions were identical to those used in the 1975 survey. The following questions on asthma symptoms were asked: 'Does your chest ever sound wheezy?', followed by 'Does this wheezing happen only with colds?' Further questions involved frequency of wheezing, and also separately the presence and frequency of what was considered asthma, either based on a previous medical diagnosis, or opinion of the subject and family. According to the responses to these questions, the students were grouped into the following categories. The category names in brackets are those originally devised by Stanhope *et al* and are important for our comparison.

(1) No history of asthma or wheeze.

(2) Previous wheeze only with colds—one or more episodes of wheeze, not labelled asthma, but only in association with a cold, and occurring before the last year (inactive wheeze).

(3) Current wheeze only with colds—one or more episodes of wheeze not labelled asthma occurring during the last year, but only in association with a cold (active wheeze).

(4) Previous wheeze—one or more episodes of wheeze not labelled asthma, but not just associated with a cold, and occurring before the last year.

(5) Current wheeze—one or more episodes of wheeze not labelled asthma, but not just associated with a cold, occurring during the last year (subclinical asthma).

(6) Previous asthma—one or more episodes labelled as asthma by the student, but occurring before the last year (inactive asthma).

(7) Current asthma—one or more episodes labelled as asthma by the student occurring during the last year (active asthma).

Information on smoking was ascertained at the school interview. Those who had smoked at least one cigarette within the last month were defined as current smokers. Each student was also asked if he/she had ever had pneumonia or bronchitis, and a list of all medications used within the last month was requested on the home questionnaire.

Socioeconomic state was rated by father's occupation using the Congalton-Havighurst scale.[8] This scale provides a series of levels from one (highest) to seven (lowest), with the addition of an eighth level for parents either absent or not working. The eighth category was excluded in the calculation of the median score. This format was similar to that followed in the earlier survey.[9]

Ethnicity was determined by the question 'What is your ethnic origin?', with prompting of the possible responses of one or more of: European, New Zealand Maori, Pacific Island Polynesian, or other. In this analysis of both surveys, Maoris include all those who reported at least part Maori origin, and non-Maoris the remainder.

The forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) were measured by a Vitalgraph spirometer, which was calibrated regularly. Each subject performed at least three attempts before the best was recorded. Where relevant, bronchodilator medication was withheld for a minimum of six hours before testing. Values expressed at body temperature, pressure, and saturation (BTPS) were compared with the Knudson standard tables for 12 to 20 year olds.[10]

Chest ausculation during both normal breathing and forced expiration was performed by either RAS or LEP.

Statistical analysis of comparisons between the 1975 and 1989 subjects were made by analysis of contingency tables, or by *t* test. The frequencies of reported respiratory symptoms and diagnoses that were compared between the two surveys were adjusted for age, sex, and race by multiple logistic regression. The age groups both of 12 year olds and those older than 16 years included very few subjects, and so for analysis, 12 and 13 year olds were combined to form one group, as were those 16 years and older. FEV$_1$:FVC ratios and FEV$_1$ values (expressed as percentage of the predicted value) were ranked then compared with analysis of variance as a non-parametric test.[11]

Ethical approval was given by the Wellington Hospital research ethical committee. Permission to undertake the study was given by the school board of trustees of Wairoa College, and consent was gained from the parents or guardians of all participating students.

Results

The response rate to question and examination in the current survey was 87·2% of 499 third to fifth form students (age 12–18 years) attending Wairoa College. Details of the participants are shown in table 1. Of the 64 non-responders, eight were accounted for by personal or family illness. The remainder did not respond to repeated personal, telephone, or mail requests.

Table 1 Population characteristics

	1975	*1989*
No participating	715	435
Males (%)	50·9	54·5
Age range in years (mean)	12·4–18·7 (14·7)	12·4–18·9 (15·0)
Mean years lived in district	11·7	11·2
Median socioeconomic score*	5·7	5·7
Maori (%)†	66·8	75·4

*According to the Congalton-Havighurst score.
†Includes those of both full and part Maori origin.

DEMOGRAPHY

The median socioeconomic score was the same as in the earlier survey (table 1). When comparing each of the score levels between the two surveys, however, there was a significantly smaller number in the lowest level (n=7) in 1989 compared with 1975 (4·1% compared with 12·3%). In contrast there was a significantly larger number in the special category 8 in 1989 (21·8% compared with 13·0%), which in 1975 included two unemployed (0·3%), but in 1989 included 29 unemployed (6·7%) (p=0·0001).

The percentage of students identifying as being of part or full Maori origin was significantly more in 1989 than in 1975 (p=0·005) (table 1). In our survey 98·1% of non-Maoris were full European, and the remainder were of at least part European origin.

ASTHMA AND WHEEZE

For each of the categories involving either asthma or wheeze the prevalence was greater in 1989 than in 1975, with the exception of wheezing only with colds. The prevalence of any identified wheeze (with or without a diagnosis of asthma) significantly increased from 26·2% in 1975, to 34·0% in 1989 (p=0·01). This obervation remained true when the comparison was confined to current wheeze (with or without a diagnosis of asthma) (p=0·05). The overall increase in wheeze was mainly in the current or previous asthma categories, with a rise from 7·9% in 1975 (current 5·0%, previous 2·9%), to 13·3% in 1989 (current 8·0%, previous 5·3%, p=0·004). There was also a significant increase in the proportion reporting wheeze unrelated to colds, without a previous diagnosis of asthma (4·6% to 8·0%, p=0·01). If the definition of asthma was extended to include those who wheezed at times other than with a cold, but had had no previous diagnosis of asthma, there was in 1989 still a significantly greater proportion of asthmatics (21·4% in 1989 compared with 12·6% in 1975, p<0·0001). There was no significant change in the proportion reporting wheezing associated with colds without a diagnosis of asthma (12·7% in 1989 compared with 13·6% in 1975) (table 2).

In 1989, 35 (8%) reported that they had taken medication for asthma within the previous month, whereas in 1975 only 17 (2·4%) stated they were taking treatment for asthma.

The increase in prevalence of symptoms overall occurred in both the Maori and non-Maori groups, but was more pronounced in the Maori group. The proportion of Maoris with asthma or wheeze increased from 27·1% to 36·2% (p=0·01). The increase was less in non-Maoris (24·2% to 27·4%) and did not reach significance.

In 1989 there were four subjects (0·9%) found to have clinical wheezing, on forced expiration. This was not signficantly different from 1975, when there were seven subjects (1·0%) with clinical wheezing (JM Stanhope, unpublished data).

Table 2 Categorised responses to survey questionnaire. Results are number (% of total)

	No history of asthma or wheeze	*Asthma diagnosed*		*Asthma not previously recognised but:*				*Total*
		*Previous**	*Current†*	*Wheeze associated with a cold only*		*Wheeze without a cold*		
				Previous	*Current*	*Previous*	*Current*	
1975	528 (73·8)	21 (2·9)	36 (5·1)	22 (3·1)	75 (10·5)	0	33 (4·6)	715
1989	287 (66·0)	23 (5·3)	35 (8·0)	9 (2·1)	46 (10·6)	5 (1·1)	30 (6·9)	435

*Before the past 12 months only; †within the past 12 months.

ASSOCIATED FEATURES

A history of bronchitis was reported in 16·1% in the current survey, which was not significantly different either in total from the earlier survey (16·2%), or when each symptom category was compared (table 3).

Previous pneumonia was reported significantly less often in 1989 compared with 1975 (5·5% compared with 15·1%, p=0·0001) (JM Stanhope, unpublished data). This trend was identified in both symptomatic and asymptomatic groups (table 3).

Current smoking was significantly less reported in the 1989 survey than in the 1975 survey (p<0·0001). This trend occurred in both symptomatic and asymptomatic groups (table 3). A more detailed analysis of smoking habits over the time period will be discussed in a further paper.

The percentage reporting winter coughs of at least four weeks' duration had not changed (JM Stanhope, unpublished data). In each of the symptomatic and asymptomatic categories the prevalence was similar between the two surveys (table 3).

SPIROMETRY

The mean FEV$_1$ (% predicted) was 109·0% in the current survey. There was, however, no significant difference in this value between any of the asthma categories. The mean FEV$_1$:FVC ratio was 91·4%. Those reporting current asthma had a significantly lower FEV$_1$:FVC ratio (88·2%) than the combined remainder of the population (91·7%) (p=0·003). There was no difference in this ratio between the asthma categories other than current asthma (table 4).

Table 3 Proportions reporting other respiratory conditions according to asthma symptom category

	No asthma/ wheeze	*Asthma/ wheeze*	*Overall*
% Of each symptomatic category:			
Bronchitis history			
1975	11·6	29·4	16·2
1989	9·1	29·7	16·1
Pneumonia history			
1975	14·0	18·1	15·1
1989	4·5	7·4	5·5
Prolonged winter cough*			
1975	6·6	15·5	9·0
1989	5·1	16·9	9·2
Current smoking†			
1975	42·4	54·5	45·6
1989	29·6	41·9	33·8

*≥4 weeks per year: †at least one cigarette smoked within the previous month.

Table 4 Mean spirometric values for 1989 population. Results are % (SD)

Asthma categories	*FEV$_1$ predicted**	*FEV$_1$:FVC ratio*
No wheeze	109·3 (11·9)	91·8 (4·8)
Previous asthma†	107·8 (10·5)	91·4 (6·2)
Current asthma‡	105·8 (13·3)	88·2 (7·3)
Previous wheeze, only with colds§	109·2 (10·1)	92·6 (4·8)
Current wheeze, only with colds	110·9 (11·2)	90·5 (5·1)
Previous wheeze without colds	103·6 (9·3)	92·2 (5·7)
Current wheeze without colds	109·1 (12·7)	92·0 (5·3)

*According to tables by Knudson *et al.*[10]
†Before the past 12 months only; ‡within the past 12 months; §Without previously recognised asthma.

Discussion

There are obviously several factors which make difficult a close comparison of the prevalence of asthma through two surveys 14 years apart. There is now an increased awareness of asthma and its potential seriousness among both doctors and the wider community. Differences in cultural and socioeconomic characteristics of populations being compared may also contribute to doubt over the validity of results. Prevalence rates may differ between the different cultural groups, which are partly explained by differences in the understanding of, and interpretation of, questionnaires. There is no universally agreed definition of asthma nor a 'gold reference standard' test for asthma in survey work, and methods used 14 years apart are often not identical.

In 1982 Mitchell attempted to provide a comparison of asthma prevalence over time, in a population of 11 to 13 year old children living in an urban area in New Zealand.[12] He performed an identical study to that done by Milne in 1969,[13] and from these findings concluded an increase in asthma prevalence from 7·1% to 13·5% in this population. The racial and cultural structure of the group had however changed considerably over this time period, with a significant influx of immigrant Pacific Islanders to the area. This, along with the simplicity of the questionnaire involving just one question of 'Has this child suffered from asthma?' throws doubt on the validity of this conclusion.

In the present survey the methodology was almost identical to that of the earlier survey, and as the cultural and socioeconomic characteristics of the population have changed little with time, a valid comparison can be made. We have made our comparisons using the categories employed by Stanhope *et al*, but our results can be grouped according to currently acceptable criteria. In this paper we have presented the data obtained from questionnaires and spirometry. The prevalence of bronchial hyperresponsiveness and atopy and their association with symptoms will be dicussed in a subsequent paper.

Our survey questionnaire differed only

slightly from that used in 1975. The difference concerned ethnicity. The question asked in 1975 is now not culturally appropriate and for our 1989 survey we used the more general question on ethnic origin as in our national census. The general ethnic information sought by the question in each survey however was similar.

The 1975 survey was performed during April and May and our 1989 survey in August and September. As the questionnaires requested information on symptoms occurring both at any time previously and more specifically over the last year, however, the timing would have at most only a minor influence on responses. This difference in timing does however account for the slight difference in mean age between the two surveys. The school survey population is smaller than in 1975 just as New Zealand's population in this age group had decreased.

In the Wairoa adolescent student population the prevalence of any symptom of asthma or wheeze has increased by about 30% over the past 14 years. Within the symptomatic group there is an increase of nearly two thirds among those with a previous diagnosis of asthma, which is repeated in the group reporting wheezing other than with a cold, but with no previous diagnosis of asthma. In contrast, however, there is no difference in those reporting wheezing only with colds, without a diagnosis of asthma.

There was, however, an increase in students of at least part Maori origin in the 1989 survey and the incidence of asthma or wheeze increased more among Maoris than Europeans. This was taken into account by the adjustment for racial origin in the logistic regression analysis. Therefore a difference in proportion with Maori racial origin does not explain the rise in asthma symptom prevalence.

This significant increase in diagnosed asthma may be in part due to an increase in doctor awareness of asthma in the area. If the change in prevalence of asthma were due in part to a reclassification of wheezy illnesses, however, it would be expected that the numbers in the each of the non-asthma wheeze categories would have decreased proportionally, and there would be no change overall in those with any symptom of asthma or wheeze. Hill *et al* also found a large increase in reported asthma in a population of young schoolchildren between 1985 and 1988, although they found no increase in the prevalence of wheeze overall.[14] From this they concluded that the increase in the prevalence of asthma was inaccurate, and probably due to a change in diagnostic habits over the time period. In our study, although there is evidence for a slight increase in the diagnosis of asthma in those who wheeze, this does not account for our findings.

In the past there has been a tendency for asthma to be misdiagnosed as bronchitis in the paediatric age group. There has been no decrease in the frequency of bronchitis over the time period, however, as would be expected if this further change in diagnostic habits was contributing to the rise in asthma. There was a drop in the prevalence of pneumonia. This has occurred proportionally in both asymptomatic and symptomatic groups, which indicates that this once again does not reflect a reclassification of illnesses.

The proportion of the current population reporting asthma (13·3%) is consistent with the findings in Auckland, New Zealand in 1985 (14·2%), despite there being a younger age group (7–10 years) involved.[15] In Auckland the prevalence of 'any current wheeze' (within the last 12 months) was 22·2% in Maoris, which was significantly greater than in Europeans (16·1%). A similar trend was seen in the current survey with 27·1% of Maoris reporing current wheeze, and 20·6% of non-Maoris. This difference did not reach significance probably due to our smaller numbers.

The numbers using asthma treatment has also risen greatly, and in excess of the increase in asthma prevalence. This rise may reflect the improvement in medical understanding of asthma. There were three subjects on asthma medications who did not report asthma, which suggests that the asthma group may have been slightly larger had their family doctors been surveyed. The lack of increase in numbers found to be wheezing on the day may be in part explained by the increase in medications, although the numbers in this category were very small. This observation is in contrast to findings when younger age groups have been studied, when much higher numbers have been found to be wheezing when examined.[16]

Chronic cough, although a frequent symptom of uncontrolled asthma in small children, occurs far less frequently as a major symptom of asthma in adolescents and adults. The prevalence of prolonged (≥4 weeks) winter cough has not changed either overall, or within each of the two groups of those with and without asthma symptoms. This indicates that in the majority the diagnosed cause of the cough remains separate from the diagnosis of asthma. This gives further support to the conclusion of a true rise in asthma symptoms, rather than merely a reclassification of illnesses.

Our functional assessment using spirometry differed from that of Stanhope *et al* and no comparison of results between 1975 and 1989 is appropriate. We are however able to further define the current population by means of spirometry. Although there were no significant differences between asthma categories in FEV_1 values expressed as a percentage of predicted, those reporting current asthma did have a significantly lower mean FEV_1:FVC ratio than the combined remainder of the population, as may be expected among those with current obstructive disease.

In conclusion we provide evidence that the prevalence of asthma symptoms has increased among adolescents in a rural New Zealand community. This increase cannot satisfactorily be explained by a change in diagnostic classifications, as there is no fall in numbers of subjects reporting wheezing without a diagnosis of asthma. There is no change in percentages with chronic cough, particularly in the asymptomatic group, and there is also no change in numbers reporting previous bronchitis over the time period. The reason for this increase in asthma symptoms is unclear from this study. A number of hypotheses have been raised, including that of increased maternal smoking during pregnancy leading to increased fetal serum IgE concentrations and subsequent atopy.[17] Change in family size leading to a decrease in respiratory infections in early life has also been postulated as a possible contributing factor.[18] Further investigation in this area is required.

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Long term outcome of ventilated asthmatics

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Abstract

Over a 25 year period, 31 asthmatic children received artificial ventilation for acute asthma at Alder Hey Children's Hospital on 48 occasions. Altogether 47 episodes occurred from 1971–89, with no decline in the number of episodes per year (mean 2·5) over this period. Eight children died during intermittent positive pressure ventilation (IPPV), and of the 23 survivors, three further children had subsequently died from asthma. Seventeen children were followed up for more than a year after IPPV. Sixteen still had symptoms of asthma and over half had symptoms every day. Ten cooperated with pulmonary function tests: mean forced expiratory volume in one second was 83% of predicted and geometric mean provocative histamine concentration (PC_{20}) was 2·1 mg/ml. Since the follow up study a fourth patient had died from asthma. IPPV continues to be required for a small number of asthmatic children each year. The survivors remain a high risk group with significant continuing morbidity and mortality.

Intermittent positive pressure ventilation (IPPV) using mechanical ventilators was developed during the 1950s and started to be used regularly to treat acute respiratory failure during the 1960s. The first paper to describe its use in asthmatic children reported a generally good outcome,[1] and subsequent series, all from North America, have tended to show low mortality and complication rates.[2–4] No sizable European series of IPPV in childhood asthma has been reported, the largest comprising six episodes.[5] There has been no previous attempt to assess the subsequent outcome of children who survive IPPV for asthma. We report the experience of ventilating asthmatic children in a regional paediatric intensive care unit in a large children's hospital over a 25 year period. We describe the prior characteristics of children who required IPPV, the clinical course, and outcome of the episodes. Finally we document the subsequent outcome of children who survived the IPPV episodes.

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Methods

Cases were found from the register of the Regional Paediatric Intensive Care Unit of Alder Hey Children's Hospital, which has been kept since the unit opened in 1964. Case notes were consulted of all admissions to the unit for whom asthma was recorded as one of the diagnoses. Only children who were ventilated for respiratory failure due to asthma were included in the study. This yielded 31 asthmatic children ventilated on 48 occasions between November 1964 and March 1989.

The first part of the study was a retrospective survey of the characteristics of asthmatic children who required IPPV, the clinical course of the illness which led to respiratory failure, and the course and outcome of the IPPV episodes themselves. Details were extracted from the case notes by one investigator (PCS) using a proforma. If the child's regular care was in another hospital, the local hospital notes were reviewed also.

The second part was a follow up study of the children who had survived their episodes of IPPV for respiratory failure, excluding two children who were ventilated within 12 months of the study. The median duration of follow up (range) was 11 years (1·1–15·6) and median age at follow up (range) was 15 years (2·6–26·0). We first wrote to the general practitioner with a request for permission to contact the family, and a questionnaire seeking details of the patient's current symptoms and treatment. We then wrote to the patient or parents (depending on age) inviting them to attend for assessment. Those who agreed were assessed by three methods.

- A questionnaire administered personally to the patient/parents asking about their current symptoms, treatment, and strategies for dealing with a sudden severe attack.
- Spirometry, using a pneumotachograph system (Vitalograph Compact) to measure peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC). The figures used for analysis were taken from the loop with the highest sum of FEV_1 and FVC, and were expressed as percent predicted for height.[6]
- Histamine challenge, using the tidal breathing technique of Cockcroft *et al.*[7]

All asthma medications were discontinued 12 hours before assessment, except in one patient who was unable to manage without salbutamol every four hours. Three patients under 5 years old at follow up were assessed by (parental) questionnaire only. Two patients declined to attend for assessment but completed the questionnaire by post. Two patients failed to respond to three postal invitations: for these only the general practitioner assessment is available.

Results

SECULAR TRENDS

One child was ventilated in 1964 and there were

Table 1 IPPV episodes and admissions at Alder Hey for asthma, and asthma deaths in Mersey region, in two yearly periods, 1972–87

	72/73	*74/75*	*76/77*	*78/79*	*80/81*	*82/83*	*84/85*	*86/87*
IPPV (Alder Hey)	3	7	8	5	5	7	2	4
Admissions (Alder Hey)	292	410	582	716	1134	1570	1618	1679
Deaths 0–14 years (Mersey region)	NA	2	5	4	3	4	3	3

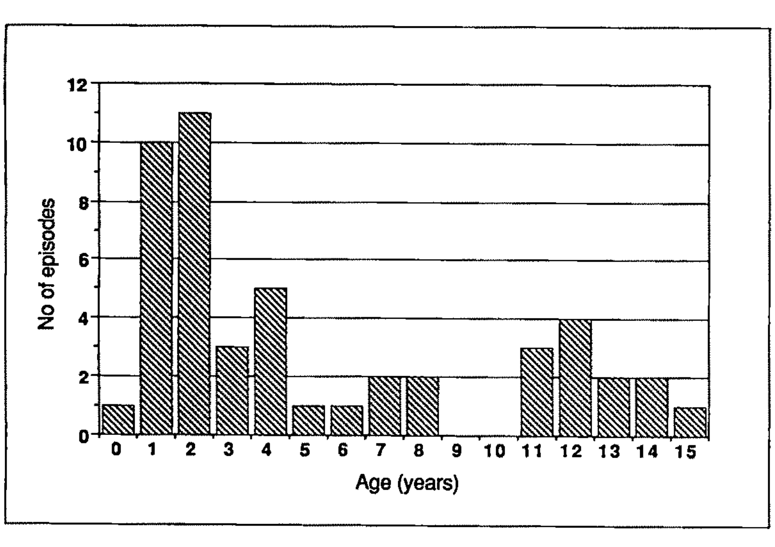
NA, figures not available.

no further episodes until 1971. Table 1 shows the number of IPPV episodes for asthma from 1972 to 1987 inclusive. There is no clear trend up or down. The total number of asthma admissions to Alder Hey over the same period has increased appreciably, as reported elsewhere,[8] and the number of childhood asthma deaths in Mersey region has remained static. The proportion of IPPV episodes after transfer from other hospitals increased from 20% between 1970 and 1979; to 64% between 1980 and 1989. The threshold for instituting IPPV has probably not altered as the arterial pH before intubation had not changed significantly between the first 10 episodes (mean 7·10) and the last 10 episodes (7·11).

PATIENT CHARACTERISTICS

The age distribution (figure) was bimodal, with the main peak at 2 years of age, very few cases in the middle childhood years, and a smaller peak in the teens. This distribution is similar to that for childhood asthma deaths in Britain,[9] but with the size of the peaks reversed. The male:female ratio was 1·2:1. The median age of asthma onset was 1 year (range 5 months to 5 years).

Most of the children had a history of frequent admissions due to asthma. Twenty of 31 had been admitted more than twice in the preceding year, eight had only occasional admissions, and three children required IPPV on their first admission. Despite this, before their first IPPV episode more than half (17/31) were receiving bronchodilators alone or no treatment for their asthma. Seven were on sodium cromoglycate, four on inhaled steroids, and three on systemic steroids or adrenocorticotrophic hormone.



Number of IPPV episodes occurring at each age.

COURSE OF ATTACK BEFORE INTUBATION

The median recorded duration of the attack of asthma before admission was 10 hours (range 0–120); 33/48 were 24 hours or less. In most cases there was no clear precipitating event for the attack; one child required IPPV after an allergen challenge, and one developed bronchospasm during a general anaesthetic.

The median interval between admission and ventilation was seven hours; 38/48 episodes progressed to respiratory failure despite at least four hours of hospital treatment. Treatment received between admission and intubation included intravenous hydrocortisone in 40/48 episodes, intravenous aminophylline in 34, intravenous salbutamol in eight, nebulised salbutamol in 15, subcutaneous adrenaline in eight, and sedatives in eight. Changes in treatment evident over the years were the disappearance of subcutaneous adrenaline (last used in 1977) and of sedatives (1979), and the appearance of intravenous (1975) and nebulised (1979) salbutamol. Surprisingly, since 1979 intravenous salbutamol had been used during only one episode, although high dose infusions have been shown capable of reversing respiratory failure in asthma.[5 10]

The decision to intubate was taken on a combination of clinical evidence and blood gases in 30 cases. For these episodes, the mean pH (SD) before intubation was 7·09 (0·1) and mean carbon dioxide tension (SD) was 11·6 (4·5) kPa. The rest had no blood gases recorded before intubation. One child was already intubated for a general anaesthetic and three were intubated on arrival at hospital after a respiratory arrest in home (n=2) or ambulance (n=1). In the remaining 14 episodes the child progressed to respiratory failure in hospital, over a median time of six hours, without having blood gases recorded. By the time they were intubated, many children had developed evidence of cerebral or cardiac hypoxia. Two had a respiratory arrest in hospital and one a cardiac arrest during intubation. Six were semiconscious, five unconscious, and two having fits before intubation.

COURSE AND OUTCOME OF IPPV

Median duration (range) of IPPV was three days (1–27). Volume cycled ventilators were used and all children received a muscle relaxant (turbocurarine chloride in 45/48 episodes) as well as sedation.

The commonest complications occurring during the 48 episodes were as follows. Lobar collapse occurred in 29 episodes (60%), and usually involved one or both upper lobes (28 episodes). Pneumomediastinum (leading to subcutaneous emphysema) was seen in 13 (27%) and pneumothorax in 10 (21%). Hypoxic-ischaemic encephalopathy developed during nine episodes, three of which had been preceded by cardiorespiratory arrest and one by hypoxic fits. None of the survivors suffered long term neurological sequelae. Transient proximal myopathy, which occurred in six episodes, has been reported previously after IPPV for asthma and is presumed to be due to steroids.[11] Inappropriate antidiuretic hormone secretion (defined as hyponatraemia and fluid retention) occurred in six episodes, five of which were associated with hypoxic-ischaemic encephalopathy.

Eight of the 48 episodes (17%) had a fatal outcome. Cardiorespiratory arrest before IPPV, and hypoxic-ischaemic encephalopathy both predicted a poor prognosis. Five of six episodes preceded by a cardiorespiratory arrest were fatal, even though in three of the five fatal episodes the arrest occurred on the intensive care unit. Six of nine episodes complicated by hypoxic-ischaemic encephalopathy were fatal, and in five of these six there was evidence of cerebral hypoxia before intubation. Blood gases before intubation, where available, did not predict outcome, but those children intubated after an arrest had not usually had blood gases recorded. None of the other complications was statistically associated with a fatal outcome.

Multiple IPPV episodes were associated with a poor outcome: of the seven children ventilated more than once, five eventually died during an episode ($p<0{\cdot}05$). Age also appeared to be a factor: the mean age at ventilation for fatal episodes (9·6 years) was significantly older than for non-fatal episodes (5 years) ($p<0{\cdot}005$). Children who had already received steroid treatment at home before their first IPPV episode were significantly more likely to die ($p<0{\cdot}05$).

LONG TERM OUTCOME

Eight of the 31 children had died during IPPV. Of the 23 survivors, three were found to have died subsequently, and one patient could not be traced. Of the 19 definite survivors, two had been ventilated less than 12 months before the follow up study. Only data from the 17 patients with at least 12 months' follow up will be presented.

Information from the general practitioner questionnaire was available for all 17 patients. One was said to be asymptomatic, nine (53%) had chronic daily symptoms, and seven had intermittent symptoms. Most patients were being prescribed prophylaxis: sodium cromoglycate in three cases and inhaled steroids in 10 (with additional theophylline in five). Three were only prescribed bronchodilators, but all three had chronic daily symptoms and clearly merited prophylaxis.

The personal questionnaire was completed for 15 patients. Nine of 15 (60%) experienced wheezing every day and two of these were constantly wheezy. Six (40%) awoke wheezing more than once a week and three were disturbed every night. Fourteen (93%) had more than 10 acute attacks per year, and five (33%) had missed two weeks of work or school due to asthma in the previous three months. Thirteen (87%) wheezed regularly on exercise.

All these patients had, by definition, suffered at least one life threatening asthma attack, and of the nine sets of parents interviewed, four had been afraid that their child would die during at least one other attack. Despite this, surprisingly few families had a clear plan of action, or additional treatment available, in the event of a rapidly developing severe attack. Five had a nebuliser at home, one having home oxygen also. One knew how to take high dose β agonist by valved spacer. The remaining nine had no contingency for dealing with a more severe attack while awaiting further help. None of the 15 had reserve oral steroids at home. Although 12 were 5 years old or more, only one had a peak flow meter at home. In the event of a severe attack, eight would contact their general practitioner initially and seven would go directly to the local hospital. Only six had an 'open access' arrangement with the hospital. Thirteen had a family car and 11 said they would use it in preference to calling an ambulance.

Ten patients attended for pulmonary function testing: their mean (SD) value as percent predicted for FEV$_1$ was 82·9 (12·9), for peak flow 98·8 (14·7), and for forced respiratory ratio 78·7 (9·5). Five had FEV$_1$ values less than 80% of predicted. Geometric mean provocative histamine concentration (PC$_{20}$) was 2·1, range 0·23 to 32 mg/ml.

LATE DEATHS

The three children who died between the IPPV episode and follow up had all suffered from severe asthma since early childhood and were on long term systemic steroids. Since completing the study we have learnt of one more death (case 4). In all four cases the fatal incident was clinically a rapidly progressing asthma attack, though only one child (case 2) had a postmortem examination. This showed typical changes of acute on chronic severe asthma. The details of these four children are summarised in table 2.

In all, nine of the 28 children who survived

Table 2 Details of children who survived IPPV but died subsequently

Case No	*Age at asthma onset*	*Age at IPPV (years)*	*Age at death (years)*	*Regular treatment*	*Manner of death*
1	6 months	12	14	Prednisolone, isoprenaline, ephedrine	Acute asthma at home
2	9 months	2	3	Prednisolone, beclomethasone, sodium cromoglycate, theophylline, salbutamol	Acute asthma at home
3	14 months	2	3	Prednisolone, beclomethasone, aminophylline, salbutamol	Acute asthma in hospital
4	3 years	12	15	Budesonide, theophylline, salbutamol	Respiratory arrest at home; IPPV discontinued after one week (brain dead)

their first IPPV episode have subsequently died from their asthma, at median (range) 1·6 years (0·5–8·4) from their first IPPV.

Discussion

The treatment of asthma has changed considerably since 1964, and this was apparent among our ventilated patients. With more effective treatment available, one might expect the numbers of asthmatic children requiring ventilation to decline, but in our regional intensive care unit this is not occurring. This is probably because over the same period, admissions for acute asthma have increased considerably, so that in fact the proportion of admissions requiring ventilation has declined. An increase in tertiary referrals may also have contributed.

Asthmatic children who require IPPV tend to be either the very young or teenagers, to have developed asthma at an early age and required multiple admissions, have an equal sex distribution (in contrast to the overall male predominance in childhood asthma), and have been previously undertreated. In all these characteristics they resemble children who die from acute asthma,[9 13 14] and indeed our follow up showed a high incidence of further IPPV episodes and of sudden death from asthma. There may be different mechanisms that predispose preschool and teenage asthmatics to respiratory failure. Young children have intrinsically narrower airways, may develop respiratory muscle fatigue more readily, and are less responsive to bronchodilators. Adolescents tend to comply poorly with treatment, may start to smoke, and may deny symptoms and therefore present later to hospital. The three children who presented to hospital after a respiratory arrest were aged 12, 14, and 15 years.

Asthmatics who survive IPPV tend to continue to have daily symptoms and considerable life disturbance, and although many experience further life threatening episodes, few have either a clear plan of action or extra treatment available at home to cope with a severe attack.

In the four large published series (comprising 19 to 30 episodes) of ventilated asthmatic children, all American, the mortality rate ranged from 0% to 5·3% of episodes.[1–4] In our series mortality was considerably higher, eight of 48 episodes (17%) being fatal. No consistent differences were apparent between the American centres and Liverpool in management during IPPV, but in the American series the threshold for instituting IPPV appeared lower, and hence the ventilated children less severely ill. In Seattle for example, 5·3% of all acute asthma admissions received IPPV (0·6% in Liverpool), mean pH before intubation was 7·22 (7·09 in Liverpool), and 5% of IPPV episodes followed a respiratory arrest (10% in Liverpool).

We are still ventilating two to three asthmatic children per year, and it seems likely that IPPV could be avoided in some of these by improved medical management. Among the children we are ventilating, mortality appears unacceptably high, and is most commonly related to hypoxic-ischaemic encephalopathy before IPPV. Much of this was occurring in hospital, and again should be preventable. The main inadequacies identified by our study were inconsistency in management (for example, failure to start steroids early), reluctance to use intravenous β agonists, reluctance to measure blood gases, and failure to diagnose respiratory failure early. We have attempted to correct these deficiencies by introducing a written protocol for inpatient management of acute asthma by junior staff. Early clinical diagnosis of hypoxia and respiratory failure is essential but difficult, and to measure arterial blood gases on all asthmatic children admitted would be neither practicable nor desirable. Semiobjective clinical scoring systems have been advocated,[12] but have not been proved to be of value. Pulse oximetry, now becoming more widely available, should allow earlier detection of hypoxia.

Ventilation is still required during some episodes of acute asthma despite improvements in the treatment available. Improved monitoring of children admitted with acute asthma and intensive treatment of early respiratory failure are neccessary to reduce the need for IPPV and avoid hypoxic brain damage. Survivors continue to suffer from severe chronic asthma and are at risk of sudden death from their disease. They require close follow up into adult life and must have a clear action plan for acute attacks.

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Commentary

Mortality from asthma in the United Kingdom is unchanged or even rising,[1] despite the advent of new drugs, more publicity, greater critical appraisal of treatment policies, earlier hospital admission, and the wider availability of mechanical ventilation (IPPV). The asthmatic process is reversible in a high proportion of patients and mechanical ventilation should, in theory, buy time for other measures to take effect. Nevertheless, most series describing the outcome of IPPV for severe acute asthma in adults record a significant mortality$^{2-6}$ and identify avoidable factors.$^{7-9}$ Against this background, it is pertinent to examine data for asthmatic children requiring IPPV and reported here from Alder Hey Children's Hospital.

Seddon and Heaf's results make depressing reading. Forty seven episodes of mechanical ventilation were required by 31 children, most around the age of 2 years but with a smaller peak in the teenage years. Approximately two thirds had been admitted more than once in the preceding year and only three children needed mechanical ventilation on their first admission. Despite this, more than half were receiving either no treatment or bronchodilators alone before their first episode of IPPV.

Eight children died during IPPV, five deaths occurring in patients who had required IPPV on an earlier occasion. Six suffered a cardiorespiratory arrest before intubation, three outside hospital but another three who were already in the intensive care unit. Five of these six children died.

Those intubated after an arrest had usually not had blood gas tensions measured. Fourteen children in whom there were no arterial blood gas measurements before intubation progressed to respiratory failure, in hospital, over a median time of six hours. By the time they were intubated, many had evidence of cerebral or cardiac hypoxia. Two suffered a respiratory arrest and one a cardiac arrest during intubation. Six were semiconscious, five unconscious, and two having fits before intubation.

Hypoxic-ischaemic encephalopathy developed during nine episodes of IPPV, three of which had been preceded by a cardiorespiratory arrest and one by hypoxic fits. Six of these nine instances proved fatal. There was evidence of cerebral hypoxia before intubation in five of the six.

Respiratory complications were seen too, lobar collapse in 29 episodes (60%), pneumomediastinum in 13 (27%), and pneumothorax in 10 (21%). Acute circulatory impairment or collapse after the institution of IPPV is the only complication recognised in adults but not included in this series.$^{7\ 8\ 10-12}$

A novel and welcome feature of this report is that the authors explored the subsequent progress of their subjects. Here too their findings are sombre. Four more children have died, all from a rapidly evolving attack of asthma. Sixteen of 17 survivors followed up for more than a year continued to suffer asthmatic symptoms, which were present every day in more than half of them.

The conclusions are clear. IPPV is needed for a small number of asthmatic children each year. Avoidable deficiencies of management and an unacceptably high incidence of hypoxic complications have been identified. Survivors remain a high risk group in need of long term supervision and counselling, with a clear action plan agreed for handling an acute attack. As a result of these findings, a written protocol has been introduced at Alder Hey to improve the service and reduce mortality in future.

Seddon and Heaf are to be congratulated for their tenacity in gathering this data which covers a 25 year span, for their honest reporting of deficiencies in management, and for reminding us that there is a small, high risk group of asthmatic subjects for whom 'too little, too late' can easily prove fatal. Above all they are to be congratulated for their constructive and practical attempt to identify how services for these vulnerable young patients can be improved in the future.

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Cerebral palsy: why we must plan for survival

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Abstract

The survival of children in the South East Thames region, born between 1970 and 1979 and diagnosed as having some form of cerebral palsy was investigated. Of the 732 children studied, 651 (90%) are still alive, and hence cerebral palsy must be regarded as a condition with which people live rather than a condition of which they die. Survival varies considerably among the different diagnostic groups: those suffering from spastic quadriplegia, dyskinetic and 'mixed' cerebral palsy are most severely affected. Our evidence suggests that, though immobility and severe mental subnormality are the strongest predictors of mortality in children with cerebral palsy, the majority of even the most severely affected patients survive to adulthood. It is therefore appropriate to plan for their survival by funding and evaluating programmes to maximise health, independence, and quality of life.

Cerebral palsy is costly. In recent years doctors have become increasingly aware of the rising cost of settlements in cases in which it was considered that the condition was caused by medical negligence; the consequent escalation in subscriptions to medical defence organisations; and the introduction of new arrangements to indemnify doctors working within the NHS. Most doctors have little contact with affected persons and their families, however, and can only imagine the other financial and personal costs.

Despite the paucity of published information on the life expectancy of patients with cerebral palsy, services that will maximise the quality of life of survivors need to be planned and resourced. Researchers have followed up affected children, but typically the number of cases has been small, and in some studies the population has been selected by the need for long term institutional care.[1–3] The existence of a register of children with cerebral palsy in the South East Thames region born from 1970 to 1979 allowed us to trace cases to find out whether or not they had died, and has made possible calculations based on 732 cases covering the full range of severity. The survival of children suffering from different types of cerebral palsy and the effect of additional impairments on survival is presented.

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Patients and methods

A register of children with cerebral palsy born from 1970 to 1979 in the South East Thames region, or resident in the region at the time of ascertainment, was assembled between 1978 and 1981 using multiple sources.[4] In 1985 a follow up study was undertaken by contacting paediatricians in the region to find out the current whereabouts of the children and any change in diagnosis. In 1988 the status of each child was further established using the resources of the National Health Service Central Register (NHSCR) at Southport, through which body notification of any change in status continues to be received.

The original study comprised 816 cases, with a prevalence of about 2/1000 live births from 1970 to 1974, which suggests that ascertainment was reasonably complete in the first half of the study period. Of these 816 cases, 76 have not been included in this presentation as their diagnosis was uncertain or was revised by the paediatrician responsible for their care: 14 of them were described as having become clinically normal, in 49 a diagnosis or provisional diagnosis of cerebral palsy was revised, and in 13 cases it has not been possible to confirm a provisional diagnosis. Though it might not be correct to exclude all these cases from the calculation—for example—of trends in prevalence, we considered it appropriate to exclude them from the analysis of survival.

Sixteen cases were excluded for administrative reasons: two of the children had resided only briefly in the region, two had been notified twice under different names and from different parts of the region, and two born in 1980 had been included under incorrect dates of birth. A further 10 cases could not be traced by NHSCR and hence could have been duplicates, so were excluded. This left 724 of the original 816 cases, and to these have been added a small number of new cases that were ascertained only after they had died. In 1986 a search of death certificates to find additional cases of cerebral palsy was undertaken by the Office of Population Censuses and Surveys (OPCS) on our behalf (1970 to 1974 births only), and yielded seven new cases. One further case was found by reference to a district deaths register. Of these eight cases, three had died aged less than 3 months, and none was aged more than 2 years at death. After the exclusions described, the new cases brought the total number of children included in the present analysis to 732. Survival analysis was done by standard methods, computer programs BMDP1L and BMDP2L.

Results

Of the 732 cases, 73 had died and 651 were listed as alive at the end of December 1989, although the possibility of a delay in notification of a death to us by NHSCR cannot be excluded. Eight cases were lost to follow up on a known date—for example, when moving overseas; as these cases have a known duration of survival it is possible to include them with the 'alive' group in the analysis of survival.

SURVIVAL BY YEAR OF BIRTH

Survival by year of birth is shown in table 1. The smaller number of cases in the later years illustrates the point made in the earlier paper that though ascertainment was considered virtually complete in the earlier years, this was not so for the later years.[4] The high percentage of deaths in children born in 1979 may be accounted for by the fact that the more severely affected cases were most likely to have been firmly diagnosed as having cerebral palsy before the study period ended in 1981, when they were still relatively young.

RELATIVE RISK OF DEATH CALCULATED USING NATIONAL DATA

There are 420 boys and 312 girls who have an average of 15·0 years of follow up (16·0 years for those who have not died) covering the ages 0 to 19·9 years. Forty seven boys and 26 girls died, while 11·5 and 6·4 deaths, respectively, would have been expected if death rates in the general population data for England and Wales, 1970–2 had applied. In the first year of life the number of deaths was lower than expected for both boys and girls, but from the ages of 1 to 19 the numbers are much higher: 41 boys and 22 girls compared with the expected 3·20 and 1·67 (fig 1).

Table 1 Survival of cases of cerebral palsy by year of birth

Year of birth	*No alive*	*No lost to follow up*	*No (%) dead*	*Total*
1970	85	1	16 (16)	102
1971	106	1	11 (9)	118
1972	95	1	7 (7)	103
1973	85	1	9 (9)	95
1974	68	0	10 (13)	78
1975	59	0	2 (3)	61
1976	61	2	5 (7)	68
1977	40	1	5 (11)	46
1978	33	1	4 (11)	38
1979	19	0	4 (17)	23
Total	651	8	73 (10)	732

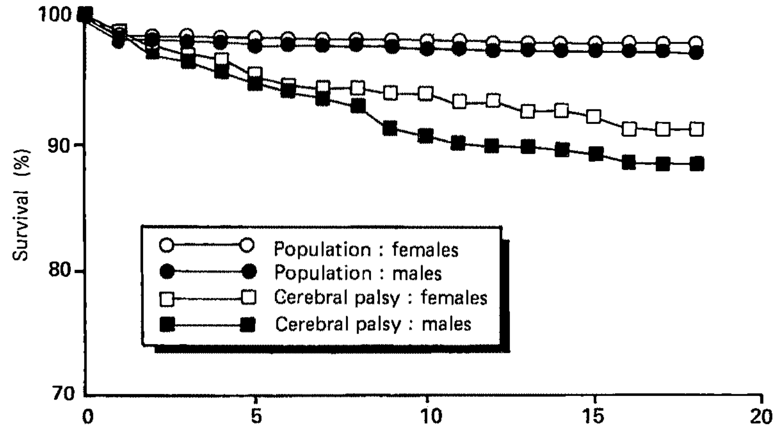

Figure 1 Comparison of survival curves for children (females and males) in the general population in England and Wales (1970–2) and children with cerebral palsy born between 1970 and 1979 in the South East Thames region.

Although the death rate among boys is higher than that among girls, the difference is not statistically significant, and is in line with the male-female difference in the general population. Though there is considerable fluctuation from year to year, there is no evidence of any trend up or down in this relative risk from the age of 1 to 19 years in either sex, though the number of deaths is too small to draw firm conclusions.

FACTORS AFFECTING SURVIVAL

Type of cerebral palsy

The cases subdivided by type of cerebral palsy are shown in table 2. In most cases this is based on the diagnosis given by the paediatrician responsible for each child's care in the original study, although in a few cases this has been enhanced by additional information obtained from the death certificate. Most of the deaths (67% of those in which the type of cerebral palsy is known) occurred in the spastic quadriplegia (and tetraplegia) group, the children commonly having additional impairments, especially in mental ability. Their impaired survival is, however, only in part attributable to the association with severe subnormality (see multivariate analysis below). The survival of cases in this and two other diagnostic groups is shown in figure 2. In view of the fact that spasticity is not always mentioned if another type of cerebral palsy is also present, we did not consider it appropriate to present the results for the ataxic or dyskinetic children separately from the ataxic spastic or dyskinetic spastic children. The unsatisfactory term 'mixed' is used to describe a small group of cases: this can mean different things to different people, and clinicians do not always specify the 'ingredients' of the 'mixture' when using it to describe cases. We have used it to cover those who have a mixture of ataxia and some sort of dyskinesia, often with spasticity. Most suffer from additional impairments, and this group has an appreciably reduced survival rate (table 2).

Table 2 Deaths by type of cerebral palsy

	No (%) alive or lost to follow up	*No (%) dead*	*Total*
'Hypotonia'*	10 (91)	1 (9)	11
Hemiplegia/monoplegia	153 (99)	2† (1)	155
Diplegia/paraplegia	100 (100)	0	100
Quadriplegia	107 (74)	37 (26)	144
Ataxic (with or without spasticity)	64 (98)	1‡ (2)	65
Dyskinetic (with or without spasticity)	108 (91)	11 (9)	119
'Mixed'	9 (75)	3 (25)	12
Type not known	108 (86)	18 (14)	126
Total	659 (90)	73 (10)	732

*Not necessarily hypotonic cerebral palsy.

†In one case the cause of death was certified as accidental; the other had spina bifida and hydrocephalus in addition to a hemiplegia.

‡Spastic quadriplegia with ataxia, plus hydrocephalus.

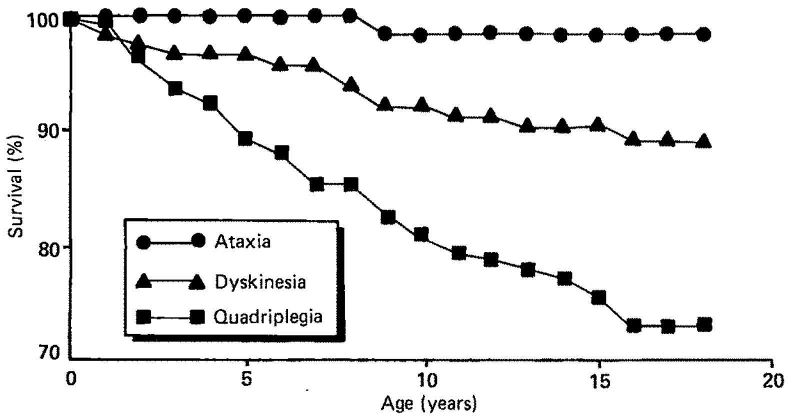

Figure 2 Survival curves for children with the three types of cerebral palsy born between 1970 and 1979 in the South East Thames region.

Table 4 Deaths by mobility and mental ability (444 cases with complete data)

	No (%) alive or lost to follow up	*No (%) dead*	*Total*
Immobile and severely subnormal	65 (69)	29 (31)	94
Immobile but not severely subnormal	27 (93)	2 (7)	29
Severely subnormal but not immobile	59 (97)	2 (3)	61
Neither immobile nor severely subnormal	258 (99)	2 (1)	260
Total	409 (92)	35 (8)	444

Mental ability

In 504 of the 732 cases an assessment of mental ability was available, and no child known to have normal mental ability has died. Table 3 shows the number of deaths that have occurred in each mental ability group. The effect of mental ability on survival is further discussed in the section on multivariate analysis.

Mobility

Mobility (as assessed in the original study when the oldest child was aged less than 12 years) is known in 453 cases, and is a function of both physical and mental factors. Of the 124 children who were confined to bed, or to a wheelchair that they did not propel themselves ('immobile'), 31 (25%) are dead. There have been only four deaths in the remaining 329 children known to be mobile. The degree of mobility of 38 children who have died is unknown; 15 of them died aged 18 months or less, so their mobility is likely to have been limited by age notwithstanding other factors. The strong association between immobility and severe subnormality leading to appreciably impaired survival is shown in table 4, and discussed in the section on multivariate analysis.

Seizures

Preliminary univariate analysis demonstrated an association between the presence of epilepsy and reduced survival. This finding is, however, the result of the strong association between epilepsy and mental subnormality. It is possible that future analyses that discriminate between seizures that occur only early in life, and persistent seizures, may elucidate any effect on survival, but these data are not available at present.

Table 3 Deaths by mental ability (504 cases)

	No (%) alive or lost to follow up	*No (%) dead*	*Total*
Normal	111 (100)	0	111
Slight impairment	84 (97)	3 (3)	87
Moderate impairment	112 (96)	5 (4)	117
Severe impairment	149 (79)	40 (21)	189
Total	456 (90)	48 (10)	504

Hydrocephalus

The original assessment did not include a specific question regarding the presence or absence of hydrocephalus, but its presence was mentioned in 30 cases, of whom eight (27%) are now dead. Of the remaining 702 cases who are not known to have hydrocephalus, 65 (9%) are dead. Of the eight cases with hydrocephalus who died, six are known to have been severely subnormal, and mental ability was not known in the remaining two cases; three were immobile, one had limited mobility, and mobility was not known in the four remaining cases. In each case the death certificate included a reference to hydrocephalus.

Birth weight and sex

So far data analysis has shown that in those children who survive the first few months of life, neither birth weight nor sex has any important impact on survival to the age of 18.

'Anticipated future prospects'

When originally assessing children for the study, paediatricians were asked to express an opinion on 'anticipated future prospects'. Of the 732 cases in the current analysis, an opinion was expressed for 438 cases, of whom 173 (39%) were expected to require permanent care. Of these, 145 (84%) are still alive.

MULTIVARIATE ANALYSIS

There were 444 patients for whom data were sufficiently complete to permit multivariate analysis, and of these 35 (8%) have died. Using proportional hazards regression, the effects of mobility, mental ability, seizures, sex, and birth weight were examined together. The results are expressed as risks for those with a factor relative to those without the factor. This showed that immobility and severe mental subnormality were the two strongest predictors of mortality, and they both made contributions independently of the other. Using the 'mobile' cases to determine the baseline value, being 'immobile' is associated with a relative risk of 10·8 (p=

0·0001, 95% confidence interval (CI) 3 to 34); being severely subnormal has an independent relative risk of 4·7 (p=0·01, 95% CI 1·5 to 14·7). Among the group of 94 children suffering from both immobility and severe mental subnormality there have been 29 deaths (0·59 expected), and the cumulative death rate calculated using life table analysis is 33%. There is evidence that diagnostic category is also relevant, so that for those children with spastic quadriplegia who are both immobile and severely subnormal the cumulative death rate is nearly 43%. There was no important additional contribution from the presence of seizures, sex or birth weight. (Birth weight was unavailable in 117 of the 444 cases.)

CERTIFIED CAUSE OF DEATH

Copies of death certificates have been received from NHSCR for all 73 deaths. Mention of a condition classifiable as cerebral palsy appeared somewhere on 45 of the death certificates (62%), but only 16 (22%) of the death drafts had 'Infantile cerebral palsy' (International Classification of Diseases code 343-) as the underlying cause of death; this includes two cases where the wording on the death certificate was 'cerebral birth anoxia'. The small proportion of cases coded 343- means that cerebral palsy is grossly under-represented in the available mortality statistics for England and Wales, which, except for 1985 and 1986, include only the underlying cause of death and not multiple causes.

Epilepsy featured in 14 (19%) death certificates, and mental subnormality in 15 (21%). In 57 cases (78%) there was a respiratory (or cardiorespiratory) cause of death, most commonly a respiratory infection. It should be noted that these figures are not mutually exclusive. A full description of the information on causes of death will be published separately. It is worthy of note, however, that chickenpox, measles, and pertussis appeared as a cause of death in one case each.

Discussion

Most of the children (90%) are still alive, and are now aged between 10 and 20 years. The widely differing prospects of the diagnostic groups underlines the need for a generally accepted method of describing the motor deficit in affected children to sharpen the focus.[5] The present diagnostic 'anarchy' is clearly unsatisfactory, and clouds discussion not only of future prospects but also regarding possible aetiologies.

'Cerebral palsy' is a diagnostic label that is usually applied only after some weeks or months of investigation and observation. Hence children who died in the first few months of life were less likely to have been defined as 'cases'. This means that the total number of deaths occurring in the first year of life is artificially low, and gives a risk of death for this period that is lower than that of the general population.

Of the children with cerebral palsy born in the early 1970s, about 85% of those who survived the first few months of life may be expected to reach the age of 20 years. The high proportion of survivors in all groups, even among those expected to require permanent care, is likely to come as a surprise to those (some doctors as well as lay people) who believe that most children severely affected by cerebral palsy die in the first few years of life.

Immobility and severe mental subnormality seem to be the most important factors influencing survival: where one of these factors is present survival is slightly reduced, but the effect is most pronounced when both factors are present. Eyman *et al* concluded that non-ambulation and low intelligence quotient (IQ) were associated with impaired survival in their studies of persons with mental retardation, some of whom also suffered from cerebral palsy.[6] They also reported that epilepsy was associated with impaired survival. They did not state, however, whether or not they had used multivariate analysis to eliminate any confounding effect of the association of epilepsy with non-ambulation and low IQ.

In 1983 Carter and Jancar drew attention to the increased longevity of mentally handicapped persons in hospital, which they attributed to treatment with new drugs (in particular for epilepsy), better diet, care, and environment.[7] These factors may be expected to have made an impact on the survival of children and adults with cerebral palsy. Changes in the contraindications for immunisation against some common childhood illnesses will mean that the many children with cerebral palsy who also suffer from seizures will no longer automatically be denied protection, and thus some lives may be prolonged. This is one of the many factors which need to be borne in mind when seeking to relate the survival of the children in this study to that of children being born now.

The move from institutional to community care for many handicapped children and adults has (or should have) prompted a reappraisal of their long term needs. While the debate continues regarding the value or otherwise of conductive education or other forms of intensive daily treatment, it is apparent that some children with cerebral palsy are not receiving even the most basic treatment (for example, one session a week with a physiotherapist for a child with mobility problems). This is a fact which the authors are confirming from the preliminary results of a survey of affected children born in the 1980s in the North East Thames region (PM Evans *et al*, unpublished observations).

One might reflect that further research may not necessarily produce overwhelming financial justification for greater expenditure on daily treatment programmes. If, for example, one succeeds in showing conclusively that an intensive mobilisation programme instituted as soon as a diagnosis of cerebral palsy is made reduces the likelihood of immobility in adult life, one might also show that this regimen improves the survival of those patients who, in spite of daily treatment, remain immobile and require total care, thus negating any financial benefit. It is vital, therefore, that those responsible for health care planning give appropriate weight to indices of quality of life on the part of the patient, and his or her family, when assessing the long term value of treatment.

We hope that cerebral palsy will now be regarded by all as a condition with which one lives rather than a condition from which one dies. The evidence from this study permits realistic calculations of the expected needs of children suffering from cerebral palsy, and could facilitate the long term planning of their health care at both local and national level. It also underlines the need to investigate the effectiveness of programmes designed to ensure that each patient reaches his or her full potential. Some will inevitably remain totally dependent, but where this can be avoided the necessary resources must be made available to prevent it; where it cannot the long term care needs must be properly assessed and funded.

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Human isophane or lente insulin? A double blind crossover trial in insulin dependent diabetes mellitus

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Abstract

Fifty two children with insulin dependent diabetes mellitus were randomised to receive human isophane or lente insulin preparations in combination with soluble insulin in a double blind trial. Patients were seen every two months, and crossed over after four months of treatment. Control assessed by glycated haemoglobin was significantly lower in children on human isophane insulin, but fasting blood glucose and fructosamine concentrations and the number of episodes of hypoglycaemia were similar on both regimens. In five children on twice daily insulin regimens, insulin profiles throughout a 24 hour period demonstrated greater variability on lente compared with isophane insulin despite identically administered insulin doses. A questionnaire completed at the end of the study showed that two thirds of the children and/or their parents preferred the isophane insulin, and they gave perceived improvement of metabolic control as the major reason for their choice.

Intermediate acting neutral crystalline protamine zinc insulin (isophane—also called neutral protamine Hagedorn insulin (NPH)) and insulin lente (zinc insulin) suspensions have been available for the last four decades. Both are frequently used in combination with short acting insulin in once or twice daily regimens in children with insulin dependent diabetes mellitus (IDDM). The consequences of mixing short (soluble) and intermediate acting insulins have only recently been thoroughly investigated.[1–3] In adults with IDDM studies of the absorption, metabolic actions, and changes in plasma insulin concentrations have shown that lente insulin has a more protracted action than isophane insulin due to the loss of solubility of short acting insulin in the presence of excess zinc.[3 4] There is some evidence that lente regimens may thus result in improved metabolic control in the early hours of the morning.[5 6]

Most trials that have formally compared isophane and lente insulins have been of low statistical power.[7] Furthermore, the recent change from pork to human insulin with its different absorption kinetics has again raised the question of whether these two insulins are interchangeable.[8] The only large trial comparing human isophane and lente insulins is that of Tunbridge *et al* who found no differences with respect to metabolic control or frequency of hypoglycaemic episodes between the two regimens in 82 adults with IDDM.[9] There have been no comparison studies performed in children or adolescents, however, where the absorption kinetics may be different and the C peptide status is more variable.

The aims of the present study were: (i) to compare the effects of human isophane (Protaphane, Novo) and lente (Monotard, Novo) insulin regimens on metabolic control and frequency of hypoglycaemia in children with IDDM, and (ii) to ascertain whether the children and parents participating in the study have any preference for one or other insulin regimen.

Methods

PATIENTS

Fifty two children attending the John Radcliffe Hospital, Oxford (n=29) or the Hospital for Sick Children, Great Ormond Street, London (n=23) for their diabetic care were enrolled into the study. The clinical characteristics of the children are shown in table 1. Sixteen children had detectable C peptide in postprandial blood samples at entry into the study. The insulin dose and glycated haemoglobin concentrations of these children were similar to the children who were negative for C peptide, but the soluble:intermediate insulin ratio was higher in the C peptide negative children (table 1). Thirteen children were on once daily and 39 were on twice daily insulin regimens. Forty two children were receiving pork lente or isophane insulin before commencing the study; the remaining children were receiving human insulin regimens.

TRIAL DESIGN

The trial was a double blind study with randomisation stratified for C peptide status and once/twice daily insulin regimen. Children were recruited one to two months before the beginning of the study and blood was drawn for C peptide estimation. The nature of the study was explained, techniques for syringe mixing and injection of insulin were reviewed and retaught as necessary, and children and parents were taught how to take blood samples onto filter paper for fasting blood glucose estimation. They were encouraged to achieve optimal glycaemic control before the beginning of the study.

Stratification and randomisation was performed by Novo Laboratories Ltd and the pharmacy at each hospital was provided with insulins identified by code, but not by name. At entry and every two months thereafter, fasting

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Table 1 Characteristics of diabetic children by C peptide status before randomisation

	C peptide positive (n=16)	*C peptide negative (n=36)*	*Total (n=52)*
Median (range) age (years)	10·9 (5–18)	13·1 (8–18)	11·6 (5–18)
Median (range) disease duration (years)	3·6 (0·5–14)	8·9 (4–16)	6·5 (0·5–16)
Sex (M/F)	6/10	10/26	16/36
Weight (kg)*	41 (11)	43 (15)	43 (14)
Insulin dose (U/kg)*	1·0 (0·2)	0·90 (0·2)	0·93 (0·2)
Once/twice daily insulin	5/11	8/28	13/39
Soluble:intermediate insulin ratio*	0·3 (0·2)	0·5 (0·3)	0·4 (0·3)
Glycated haemoglobin (g%)*	10·7 (1·8)	10·8 (1·9)	10·8 (1·9)
Fructosamine (mmol/l)*	4·6 (0·4)	4·1 (0·9)	4·3 (0·3)

*Mean (SD).

blood glucose, glycated haemoglobin, and fructosamine were measured. Numbers of hypoglycaemic episodes occurring in each two month period were recorded in a diary card. The episodes were graded as follows: grade 1: no action required, grade 2: extra carbohydrate required, grade 3: assistance required by relative or friend, and grade 4: medical assistance or glucagon required. Between visits, telephone contact was maintained on a monthly basis.

Five children were admitted to hospital (John Radcliffe, Oxford) for measurement of blood glucose and free insulin concentrations every two hours over a 24 hour period. They remained on their normal diet, insulin, and exercise regimen. The profiles were performed twice on each child at the end of each limb of the study.

At the end of the study, before breaking the code for insulin preparations, a questionnaire was given to each participant. Questions were categorised into two sections: the first related to perceptions about metabolic control and frequency of hypoglycaemic episodes and the second to feelings about general well being, energy levels, and irritability on each insulin regimen. Visual analogue scales were utilised in the questionnare and consisted of 10 cm lines. Each line was scored from 1 to 100 with 100 representing the extreme negative pole (for example, very grumpy, etc) and one representing the extreme positive pole. Children were also asked to indicate an overall preference for one or other regimen.

The protocol was reviewed and passed by ethical committees at both participating hospitals.

ANALYTICAL METHODS

Glycated haemoglobin was measured by the agar electrophoretic method (Corning) with an interassay coefficient of variation of 4·2%. The reference range for healthy children was 4·8–7·1 g%.[10] Serum fructosamine was measured colorimetrically (Roche Diagnostics), the interassay coefficient of variation being 2·1% and normal range 2·6–3·3 mmol/l. Blood for fasting blood glucose estimation was taken onto filter paper impregnated with boric acid. After drying samples were sent to the Bristol Maternity Hospital for subsequent assay. After elution, glucose from the spots was measured by standard glucose oxidase method. Serum C peptide concentration was measured by radioimmunoassay, the lower limit of detection being 0·03 pmol/ml. For measurement of plasma free insulin 1·0 ml whole blood was added immediately to 0·6 ml of ice cold 25% polyethylene glycol (Sigma) and samples were stored at −4°C.[11] The insulin assay used was a single antibody radioimmunoassay with charcoal separation.[12] Interassay coefficients of variation at 38·0, 49·5, 89·0, and 196·6 pmol/l were 11·0, 7·9, 13·6, and 7·9% respectively.

STATISTICAL METHODS

The primary endpoint was to ascertain whether isophane and lente insulin based regimens result in similar metabolic control as measured by glycated haemoglobin. Assuming a within individual standard deviation of 1·2 g% in glycated haemoglobin, 48 children were required to detect a difference of 0·7% with a power of 90% at a significance level of 5%.

Analysis of the data was undertaken using Statistical Analysis System (SAS Institute Inc). A two way analysis of variance was used to compare within individual values for glycated haemoglobin, fructosamine, and fasting blood glucose at the end of each treatment period, allowing for the effect of order of regimen administration. No order effect was observed, however, and therefore comparisons between the two regimens are presented using paired *t* test.

Questionnaire data were analysed by comparing visual analogue scale scores using the Wilcoxon paired sign rank test. Data are presented as median differences and interquartile ranges.

Results

Fifty one children completed the study. One child defaulted shortly after enrolment by not taking any intermediate acting insulin. Ten of the 13 children who were taking once daily insulin regimens at the start of the study were still on the same regimen at the end of the study. Three children changed to a twice daily regimen because of poor metabolic control: two while on the lente and one while on the isophane based insulin regimen.

Body weight, insulin dose, ratio of soluble to intermediate insulin, and ratio of morning to evening insulin dose at the end of each treatment period were similar on both the isophane and the lente based insulin regimens (table 2). Similarly, in the subgroup of five children admitted for 24 hour insulin profiles, there were no differences in insulin dose, ratio of soluble to intermediate insulin, or ratio of morning to evening insulin dose on the two regimens (table 3).

Mean (SD) glycated haemoglobin concentrations at the end of the isophane based insulin regimen was 11·1 (2·2) g% and at the end of the lente based insulin regimen was 12·0 (2·2) g% (table 2). The within individual difference was 0·67 g% (95% confidence interval (CI) 0 to 1·35) g% lower on the isophane than on the lente based regimen (p=0·05). This difference was similar if the C peptide positive children were excluded (0·75 g% (95% CI 0 to 1·51),

Table 2 Comparison of isophane and lente insulin regimens. Values given as mean (SD)

	Isophane insulin	*Lente insulin*
Weight (kg)	44·8 (15)	45·0 (14)
Insulin dose (U/kg)	1·0 (0·2)	1·0 (0·2)
Soluble:intermediate insulin ratio	0·37	0·4
Morning:evening insulin ratio*	2·2	2·1
Glycated haemoglobin (g%)	11·1 (2·2)	12·0 (2·2)
Fructosamine (mmol/l)	4·0 (0·7)	4·0 (0·8)
Fasting glucose (mmol/l)	8·3 (3·8)	8·8 (4·6)
Hypoglycaemic episodes (total No episodes/No children):		
Grade 1	75/17	110/23
Grade 2	141/36	177/42
Grade 3	18/8	14/9
Grade 4	9/8	9/4

*For the 39 children on twice daily insulin.

p=0·05). Fasting blood glucose was 0·76 mmol/l (95% CI −0·86 to 2·38), and serum fructosamine was 0·03 mmol/l (95% CI −0·3 to 0·33) lower on than the isophane based regimen; these differences were not significant at the 5% level.

The mean (SD) insulin and glucose values for the five children who had 24 hour profiles are shown for the two insulin regimens in table 3. Variation in insulin values as indicated by within individual standard deviation was greater in all five children on the lente regimen and variation in blood glucose values was higher in four of the five children, being highest in the morning.

The frequency of hypoglycaemic episodes was similar on both regimens: the number of grade 1 or 2 episodes was slightly increased on the lente based regimen, whereas the number of grade 3 or 4 episodes was greater on the isophane based regimen (table 2).

Forty one children completed the questionnaires of whom 40 stated their preference for insulin regimen (table 4). Twenty seven of 40 children (68%) stated that they preferred isophane to lente insulin, irrespective of the insulin regimen that they were taking at the time they completed the questionnaire (table 4). Symptoms and signs of hyperglycaemia including polyuria, polydipsia, nausea, presence of urinary ketones, and high blood glucose values were reported twice as frequently on the lente compared with the isophane based regimen. In addition, 31/41 (76%) on lente compared with 18/41 (44%) on isophane insulin regimens perceived their blood glucose values to be very erratic ($\chi^2=8{\cdot}9$, p<0·03) and only 5/41 children (12%) perceived their blood glucose concentrations to be steady between 4·5 and 9 mmol/l on the lente insulin regimen compared with 18/41 children (44%) on the isophane insulin regimen. In all, 63% of those who preferred isophane insulin gave perceived improvement of metabolic control as their main reason for the preference.

Table 4 Preference for insulin regime from retrospective questionnaire

	Insulin preference			*Total*
	Lente	*Isophane*	*'Don't mind'*	
Starting insulin:				
Isophane	1	16	5	22
Lente	4	11	3	18
Total	5 (12%)	27 (68%)	8 (20%)	40

Significantly more problems with hypoglycaemic episodes were perceived on the lente based regimen (median difference in score +12, interquartile range 0 to 38, p<0·01) and children reported lower levels of energy (median 0, interquartile range +6 to −17, p<0·01) on the lente than on the isophane insulin. Median irritability score was also higher on lente than isophane insulin (median score +0·5, interquartile range −7 to +26, p=0·07).

Discussion

This double blind crossover study in children with IDDM demonstrates lower glycated haemoglobin on an isophane/soluble insulin regimen compared with a lente/soluble insulin regimen. Although the differences in fructosamine and fasting blood glucose measurements between the regimens were small, values were lower with the isophane than with the lente based regimens and the high within individual variation in fasting blood glucose concentration renders this measure open to the possibility of a type 2 error (that is, failure to detect a significant difference when one exists) in a study of this size.

There have been few studies comparing human isophane and lente based insulin regimens in individuals with IDDM, and none have been performed in children. Our results contrast with those of Tunbridge *et al* in the only adult study with sufficient statistical power to effectively compare the two regimens who observed similar fasting blood glucose, variation in blood glucose and glycated haemoglobin on the two regimens.[9] Corcoren and Yudkin[3] and Oswald and Yudkin[7] compared isophane and lente based regimens as well as pork and human insulin regimens in adults with IDDM, and found no significant differences; however, the numbers in the subsets studied were very small.

Eighty percent of the children in this study were previously on pork insulin. Equal numbers of children were randomly allocated to receive either lente or isophane insulin at the beginning

Table 3 Mean (SD) of 12 plasma insulin and glucose estimations taken every two hours over 24 hours in five children on isophane and lente based insulin regimes

Case No	*Insulin dose (units)*				*Insulin (pmol/l)*		*Blood glucose (mmol/l)*	
	Isophane:soluble		*Lente:soluble*		*Isophane*	*Lente*	*Isophane*	*Lente*
	am	*pm*	*am*	*pm*				
1	36:4	10:4	36:4	10:4	212·4 (105·5)	189·4 (132·0)	9·6 (5·9)	11·8 (7·3)
2	20:4	12:2	23:2	10:2	185·1 (64·6)	199·9 (163·6)	9·1 (4·2)	8·7 (4·9)
3	16:0	8:0	18:0	8:0	83·2 (35·9)	85·4 (39·5)	18·5 (4·3)	14·6 (8·5)
4	26:14	18:8	26:12	16:8	160·0 (51·7)	207·4 (62·4)	7·4 (4·1)	10·3 (5·2)
5	20:6	6:2	20:6	4:2	203·1 (89·0)	205·9 (122·7)	11·0 (3·4)	3·7 (2·3)

of the study and no effect of regimen order was observed. It is unlikely that the change to human insulin affected the differences observed between isophane and lente insulins, although it is of interest to note that despite being in a trial, glycated haemoglobin rose on both regimens compared with baseline.

In this study, 30% of children were positive for C peptide. When only children negative for C peptide were included in the analysis, however, the decrease in glycated haemoglobin on the isophane insulin regimen was similar to that obtained when all children were included. It is possible that the difference between our results and those of the adult studies are due to differences in factors such as insulin absorption kinetics and the presence of a different hormonal environment in children compared with adults.

The increased prevalence of hyperglycaemic symptoms and the increased variability of blood glucose concentrations perceived by the children and parents who completed the retrospective questionnaire agree with the increased glycated haemoglobin and increased variation of free insulin and blood glucose concentrations observed on the lente based regimen. In contrast, although data from the retrospective questionnaire indicated that more problems with hypoglycaemia were perceived on the lente regimen, data collected prospectively throughout the trial showed no significant difference in the frequency of hypoglycaemic episodes between the two regimens. A possible explanation for this apparent discrepancy may be that in the questionnaire, parents and children were asked to express the degree to which hypoglycaemia was a problem on each insulin regimen using a visual analogue scale and not specifically about frequency of hypoglycaemic episodes. Thus other factors such as degree of warning before having a hypoglycaemic attack and timing of attacks may have influenced their response. More detailed study would be required to further investigate this question.

Finally, answers to subjective questions about well being, irritability, and energy levels, in addition to the fact that 67% of children chose to receive isophane insulin and only 12% chose to receive lente insulin after the end of the trial, indicate that isophane insulin is the more acceptable intermediate acting insulin for children.

We conclude that human isophane when used in a once or twice daily regimen together with soluble insulin results in better metabolic control, less diurnal variation in free insulin concentration, and is more acceptable to children than human lente insulin. We therefore suggest that this should be the intermediate insulin of first choice in the treatment of children with IDDM.

We thank Dorothy Harris for her help with assaying fructosamine and free insulin samples, Dr Julie Edge and Dr Fiona Campbell for clinical assistance and Dr R Turner for assaying the C peptide samples.

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Microbiological studies of the enterocolitis of Hirschsprung's disease

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Abstract

The results of a prospective study of 20 cases of newly diagnosed Hirschsprung's disease (nine of whom developed enterocolitis) and 10 normal controls showed no variations in the bacterial flora (including *Clostridium difficile*) in the stools of the groups studied. Viral studies showed that rotavirus was present in the stools of seven of the nine cases of enterocolitis during the episode. We suggest that Hirschsprung's enterocolitis may have a complex infective aetiology and that rotavirus plays a part.

Hirschsprung's disease (congenital intestinal aganglionosis) is an important cause of functional intestinal obstruction in childhood occurring once in every 5000 live births.[1] The most severe, potentially life threatening complication is Hirschsprung's enterocolitis, and it is estimated that 5% of patients with Hirschsprung's disease will die of it. It can occur at any time during the course of the disease, irrespective of age, sex, or method or timing of management,[2-4] and is characterised by abdominal distension, diarrhoea, fever, and hypovolaemic shock. Vomiting is an uncommon feature. The diagnosis is made clinically and confirmed radiologically showing colonic dilatation, mucosal ulceration, gastrointestinal hypermotility and sometimes pneumatosis coli—although this is less common in Hirschsprung's than in necrotising enterocolitis.

The aetiology of Hirschsprung's enterocolitis is uncertain, although many theories have been advanced including proximal colonic dilatation with resultant mucosal ischaemia and bacterial invasion,[5] and hypersensitivity to bacterial antigens.[6] More recently, *Clostridium difficile* and its toxin have been implicated,[7 8] although many healthy neonates and infants excrete toxin secreting *C difficile* in their stools.[9 10]

The aim of this study was to assess prospectively the microbiological flora (bacterial and viral) in the faeces of newly diagnosed patients with Hirschsprung's disease to find out if any changes occurred in those who subsequently developed enterocolitis.

Patients and methods

During a three year period 20 new cases of Hirschsprung's disease were diagnosed. Of these, nine subsequently developed enterocolitis. Ten normal age and sex matched control patients from the same hospital ward but not with gastrointestinal conditions (circumcision, orchidopexy, and external angular dermoid cystectomy) were also studied. No patient had suffered from, or had been in contact with, diarrhoea or vomiting before or during this admission to hospital.

SPECIMENS

Specimens of faeces were taken from all new cases of Hirschsprung's disease at their initial presentation for immediate bacteriological and viral studies to be carried out. In those who subsequently developed enterocolitis, stool samples were taken during and after the attack and similar studies carried out. Fluid collected during therapeutic colorectal lavage was also sent for study. Stools from control subjects were processed in the same way.

CULTURES

Bacterial studies

Various culture media were used to isolate potential pathogens and separate them from the large number of commensals that normally inhabit the gastrointestinal tract, including blood agar, MacConkey's agar, deoxycholate citrate agar, selonite broth, campylobacter media, and cycloserine cefoxitin fructose agar. *C difficile* toxin was sought by enzyme linked immunosorbant assay (ELISA).

Viral studies

Viruses were cultured on tissue cultures. Rotavirus was specifically sought in each case by electron microscopy.

Results

There were 17 boys and three girls with ages ranging from 5 days to 2 years (mean 8·6 months). All cases were treated initially by fashioning of a defunctioning colostomy followed by anorectal myectomy (mean age 9 months), and anterior resection (mean age 11·4 months).

Nine cases subsequently developed enterocolitis, one before diagnosis of the Hirschsprung's disease and the remainder within one month of the defunctioning colostomy. Three had further episodes after anterior resection. There was no seasonal variation in incidence, five cases occurring during the winter, two during the summer, and two during the autumn. All responded to conservative management with intravenous fluids, parenteral antibiotics, and colorectal lavage.

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Microbiology of stool cultures in 20 patients with Hirschsprung's disease and 10 control subjects

	No of positive cultures in patients with Hirschsprung's disease				*No of positive cultures in control subjects (n=10)*
	Without enterocolitis (n=11)	*With enterocolitis (n=9)*			
		Before attack	*During attack*	*After attack*	
Coagulase negative staphylococcus	10	8	9	9	10
Escherichia coli	11	8	8	9	10
Streptococcus faecalis	8	5	4	8	8
Klebsiella spp	3	4	5	4	6
C difficile	6	6	7	5	6
Bacteriodes fragilis	8	6	7	7	9
C difficile toxin	5	6	6	7	5

The results of the microbiological studies are shown in the table. None of the stool samples from the 20 patients with Hirschsprung's disease or the 10 controls grew any pathogenic organisms. Viral studies of the stools and of the fluid obtained after therapeutic colorectal washout during the episodes of enterocolitis, however, showed rotavirus in seven of the nine cases (78%). No other pathogenic organisms were identified.

Discussion

Unlike previous studies,[7 8] this study has failed to isolate any specific organism that could be implicated in the pathogenesis of Hirschsprung's enterocolitis. *C difficile* was present in over half of the cases studied and there was no variation among the groups, thus confirming previous reports that this organism is a commensal within the infant gut.[9 10] There were, however, more patients with *C difficile* toxin in the stools in the enterocolitis group, which may indirectly implicate this organism.

Viral studies showed an interesting finding, in that rotavirus was isolated from the stools of seven of the nine patients who developed enterocolitis, despite not having been detected on initial investigation. Rotavirus is the commonest cause of gastroenteritis in childhood, having a peak incidence between 6 months and 3 years of age, and being most frequent during the winter. It is resistant to gastric acid and infects mature epithelial cells in the ileum, thus replicating and impairing absorptive and transfer functions and resulting in diarrhoea. Immunological defence against rotavirus is dependent upon IgA within the gut wall. Most babies have circulating maternal rotavirus antibodies at birth, but these decrease during the first six months of life, after which the child is susceptible to rotavirus infection. Breast feeding (maternal milk contains rotavirus antibody) gives some protection to the infant.

The findings of this study suggest therefore that rotavirus plays some part in the pathogenesis of Hirschsprung's enterocolitis, as there was no evidence of contact with rotavirus in these patients either before, during, or after their admission to hospital, and indeed the signs and symptoms of enterocolitis began outside the hospital environment in all cases. It seems unlikely that the episodes of enterocolitis were 'pure' rotavirus gastroenteritis, as in no case was vomiting a symptom.

We were, however, unable to explain from our results why these children were more susceptible—and subsequently overwhelmed—by this infection with generalised systemic illnesses whereas other children with the same underlying disease were not. It may be that the children who are prone to this complication have some underlying deficiency in host defence that allows them to be overcome by rotavirus or any other invading organism, as suggested by the number of patients with enterocolitis who had *C difficile* toxins in their stools.

CONCLUSIONS

From these results we suggest that rotavirus may be implicated in the pathogenesis of Hirschsprung's enterocolitis, which may therefore have a complex infective aetiology. We recommend that children with Hirschsprung's disease undergo regular viral and bacterial stool culture at diagnosis and immediately if loose stools occur to enable early detection of infection. This would permit careful observation if the children were asymptomatic and prompt diagnosis and management to prevent progression of this potentially lethal condition.

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The reliability of height measurement (The Wessex Growth Study)

L D Voss, B J R Bailey, K Cumming, T J Wilkin, P R Betts

Abstract

The two major components of reliability are accuracy and reproducibility. Three studies of the reliability of height measurement in children are reported. In the first, a standard metre rod was used to spot check the accuracy of installation of 230 measuring instruments in one health district in Wessex, UK. The readings obtained ranged from 90·0 to 108·5 cm and showed the urgent need for the positioning of instruments to be regularly checked.

In a second study, to examine the reproducibility of height measurement, two experienced observers measured 10 young children (106·0 to 152·0 cm), three times on five instruments of different design. The observations were blind and in random order. The estimated standard deviation for a single height measurement was generally in the range 0·2–0·3 cm. Over 95% of the variance was attributable to the child, very little to the instrument or observer.

Finally, the conditions of the second study were modified to examine the effect on reproducibility of non-blind and non-randomised measurements, as usually occurs in the clinic. A lower but inevitably false estimate of the error was obtained. It is recommended that the error of height measurement, appropriately established and expressed in simple terms, be stated in every published growth study.

Quality control data, although routinely reported in the laboratory, is conspicuously absent from studies relating to growth. It is presumably felt that the measurement of height is a simple task and, provided sufficient care is taken, any error will be so small that it can be safely ignored. Hindmarsh and Brook maintain that the measurement of height can be 'extremely accurate',[1] but Tanner warns that the 'heights measured in the averagely casual clinic are useless even for accurate clinical purposes, let alone research'.[2]

Earlier this century, height measuring apparatus was necessarily crude by today's standards—the instrument recommended for use in schools was Baldwin's paper measuring scale,[3] and researchers were well aware of the variability of anthropometric data. Krogman has reviewed many studies which attempted to quantify the error.[4] Instruments today are infinitely more sophisticated, which may be why many recent growth studies make no reference to any error of measurement at all.[5–8]

There is error, however, in all measurement and the validity of growth data, both in the clinic and in research, depends critically on the reliability of height measurements. Attempts of modern researchers to establish their error of measurement have often been unsatisfactory, for two reasons. First, the conditions under which the observations were made have been inadequately described and cannot therefore be replicated by others.[9 10] Second, as Cameron pointed out, there is no commonly agreed terminology to express the error of height measurement, making cross study comparisons unnecessarily difficult.[11]

This error in height measurement has been variously expressed as coefficient of variation (CV),[1] standard deviation (SD),[9] standard error of measurement (S_{meas}),[12] or standard error of the mean (SEM).[13] The coefficient of variation is defined as $SD/\bar{x}\times 100\%$, where $\bar{x}$ is the mean of the observations. The SD of a height measurement should not vary greatly with height itself, so that as a child grows, the coefficient of variation will become smaller. The error as expressed by the coefficient of variation therefore appears to diminish when measuring taller children. In practice, however, the error may be just as large and therefore just as critical for monitoring velocity, where height increment, not absolute height, is important. SD and standard error of measurement are synonymous and can be calculated from the differences observed between two or more measurements. The SD, once established, can be applied to a *single* future measurement made under similar conditions. Where the mean of *several* measurements is used in order to reduce variability, this SD can be divided by $\sqrt{n}$ to give the standard error of the mean. (Reference to an SEM would be quite inappropriate where only *single* observations are to be made, as is commonly the case, and would give a misleadingly low estimate of the error.) This study uses the SD for a single height measurement to express the error.

The aims of the present study were to establish the reliability of height measurement by examining: (i) The accuracy of installation of height measuring instruments. (ii) The reproducibility of height measuring instruments in a rigourously controlled trial, quantifying the error in clear and simple terms and analysing the contribution made to the total variance by instrument, observer and subject. (iii) The effect on the error of varying measurement conditions.

The definitions used are:

Reliability—The reliability of growth data depends on both accuracy and reproducibility

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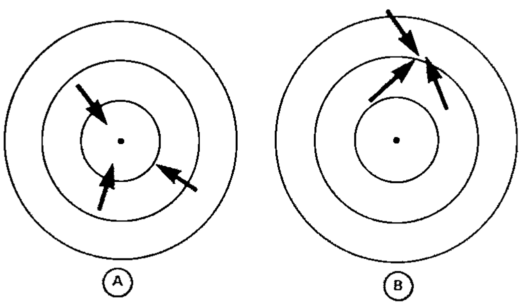

Figure 1 Dartboard analogy to illustrate the components of reliability: accuracy and reproducibility. (A) Observations are accurate but reproducibility is poor. (B) Reproducibility is good but observations are inaccurate.

(fig 1). These are quite different, yet the terms are sometimes confused.

Accuracy—This is a measure of the closeness of observations to the target, in this case the 'true' height. With an accurate instrument, the mean of a large number of observations would hit the target, irrespective of the size of their spread, provided the error is random (fig 1A). Badly installed equipment will introduce a systematic error, leading to inaccurate measurements.

Reproducibility (precision)—Repeat measurements on the same child often differ. Observations will be distributed around their mean, with some spread that could be expressed as, for example, the variance. The smaller the variance the greater the reproducibility. Measurements would be reproducible without being accurate, if the spread about their mean were small, but that mean did not coincide with the target value (fig 1B).

Sources of variance—The instrument, observer, and subject are all sources of error, and the variance of each contributes to the total variance of measurement.

Methods

(1) INSTALLATION OF HEIGHT MEASURING INSTRUMENTS

An aluminium metre rod was used by a single observer (KC) to spot check the accuracy of installation of 17 stadiometers, 55 Microtoises, 133 rulers, and 25 wall charts in everyday use in health centres, hospitals, schools, and general practice surgeries in Wessex. No prior warning was given to personnel in charge of the equipment. The recorded length of the rod was based on the mean of two readings.

The instruments examined fell into one of four groups:

Stadiometers (Holtain Ltd, Crymmych, Wales)—The 'Harpenden' model is the standard instrument in paediatric outpatient departments in the UK. It consists of a vertical backboard with a weighted horizontal cursor fixed at 90° to it. A mechanical counter running on a track records the height.

Microtoises (CMS Weighing Equipment Ltd)—A metal tape, hung from a permanent hook on the wall, is pulled down onto the child's head. It is used predominantly by peripatetic school nurses.

Ruler—Any simple vertical scale with a moveable horizontal bar was described as a ruler. These are frequently found in general practice and in schools.

Wall charts—These included any charts attached to the wall against which the child stands. A right angled block is placed on the child's head and the height read directly off the chart. They were found mainly in general practice and in health centres.

(2) REPRODUCIBILITY OF HEIGHT MEASUREMENTS—STANDARD EXPERIMENTAL CONDITIONS

Instrument and observer alone

Two blocks of machine cut wood, of different but unknown length, were measured 10 times each by a single observer on five different instruments: (a) *Holtain electronic stadiometer*—the headpiece, when horizontal, activates a light beam which then reads the height off a binary scale giving a digital readout; (b) *Harpenden stadiometer*—as described earlier; (c) *Raven Magnimetre*—the fixed backboard has a removable magnetic measuring arm; (d) *Raven Minimetre*—similar to the Microtoise, but more easily repositioned as it can be stuck to the wall with plastic adhesive; and (e) *Harpenden pocket stadiometer*—the head bar with retractable metal tape is hooked to a freestanding base plate. It is difficult to ensure the tape is taut while keeping the head bar horizontal.

The order of measurements was randomised and they were also 'blind', so that although the observer positioned the blocks and lowered the headpiece, a third party noted and recorded the readings to the nearest 1 mm. The instruments were checked for accuracy using a metre rod both at the start and at the end of the trial and were found to be unchanged.

Instrument, observer, and child

Ten children (aged 4 to 11 years, heights 106·0 to 152·0 cm) were each measured three times by two experienced observers on the five accurately installed instruments described above. These measurements were also made under standard experimental conditions—that is, blind and in random order. Conventional anthropometric methods were used throughout.[11]

(3) REPRODUCIBILITY OF HEIGHT MEASUREMENTS—VARYING CONDITIONS

In a further trial, 10 children (eight from the previous trial) were measured by two experienced observers (one from the previous trial), seven times each using just two instruments: the Harpenden stadiometer and the Raven Magnimetre. The trial was designed in such a way as to allow a comparison of the reproducibility of height measurements under three different conditions: (i) Blind, random order: the standard conditions described above were repeated. (ii) Blind, successive: the observers again measured each child 'blind', but three times in quick succession. The children were removed from the instruments between measurements but immediately replaced so that no other children were measured between. (iii) Non-blind, suc-

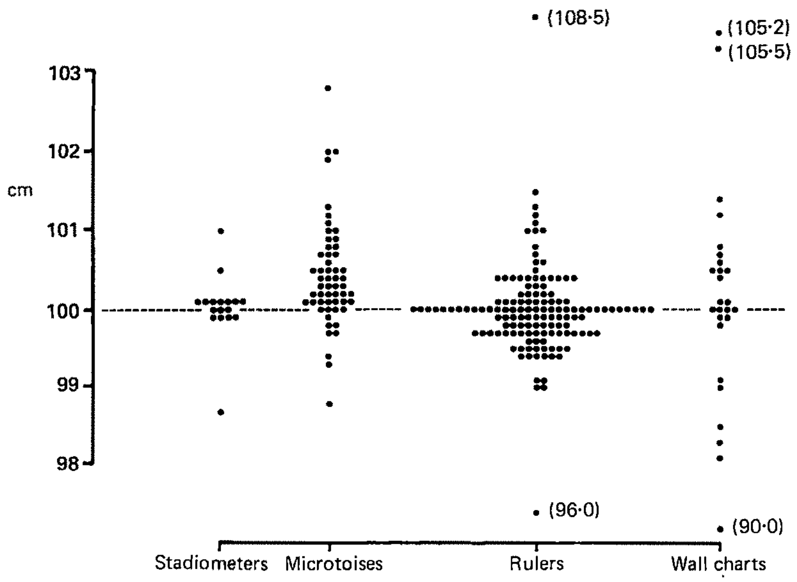

Figure 2 The length of a 100 cm metal rod as recorded by 230 measuring instruments installed in clinics throughout Wessex.

cessive: the children were measured three times in quick succession, and the measurements were no longer blind. Each observer was asked to read and record his own data.

Results

(1) INSTALLATION OF HEIGHT MEASURING INSTRUMENTS

Figure 2 shows the individual results of measuring the same metre rod, grouped according to instrument type. There were many cases of badly installed equipment. In each group there was an error of at least 1 cm above or below 100 cm; for some types of instrument, it was considerably greater.

The range of error was least for stadiometers (98·7 to 101·1 cm) and greatest for wall charts (90·0 to 105·2 cm). In the case of Microtoises, rulers, and wall charts, inaccuracies arose from positioning the instrument at the wrong height. The mean reading for the Microtoises, significantly greater than 100·0 cm ($p<0·001$), suggested a systematic tendency for these instruments to be placed too low. Incomplete extension of the tape during installation is the most likely cause. Error in the stadiometers was mainly due to incorrect setting of the digital counter on its track as a result of rough handling. Personnel using these instruments were almost without exception unaware of the inaccuracies.

(2) REPRODUCIBILITY OF HEIGHT MEASUREMENTS —STANDARD EXPERIMENTAL CONDITIONS

Instrument and observer alone

Table 1(a) shows the reproducibility of each instrument when measuring a rigid block of wood. The SD of a single height measurement was calculated. This ranged from 0·0 cm (Holtain electronic stadiometer, whose digital readout measures only to the nearest mm) to 0·1 cm (Raven Minimetre and Harpenden pocket stadiometer, where the variability, though greater, was still very small). The accuracy of each instrument, as measured by a metre rod, did not vary throughout the trial.

Table 1 Reproducibility of height measurements (standard experimental conditions)

Instrument	*(a) Instrument and observer alone SD (cm)*	*(b) Instrument, observer, and child SD (cm)*
Holtain electronic stadiometer	0·00	0·29
Harpenden stadiometer	0·07	0·26
Raven Magnimetre	0·03	0·17
Raven Minimetre	0·10	0·23
Harpenden pocket stadiometer	0·10	0·58

SDs are based on measurement of (a) two wooden blocks of unknown length and (b) 10 children, pooling data from two observers measuring each child three times on each instrument.

Instrument, observer, and child

Table 1(b) shows the reproducibility of each instrument when measuring children as opposed to wooden blocks. The SD is much greater, ranging from 0·17 cm (Magnimetre) to 0·58 cm (pocket stadiometer) when averaged over children and observers. This last instrument was significantly less reproducible when measuring children than the other four, among which there was no statistically significant difference in reproducibility ($p=0·14$). Neither was there any significant difference between the reproducibility of measurements made by the two observers, on any of the five instruments (p values ranged from 0·075 to 0·90), allowing their data to be pooled in table 1(b). The observers did, however, differ in technique and it is clear from table 2 that there was a significant difference between the two observers in mean height when using the Holtain electronic stadiometer, the Harpenden stadiometer, and the Raven Magnimetre. Where both hands were free to stretch a child, observer Y measured children significantly taller than X for all three instruments. It also follows that the height of a child may differ according to the technique involved in using different instruments. Pooling the data for the two observers, mean heights of the children were greater using the Holtain electronic stadiometer and Raven Magnimetre than when using the Raven Minimetre and Harpenden pocket stadiometer where no stretching was possible.

There was a pronounced difference in the reproducibility of height measurement between individual subjects. Looking only at the data for the Holtain electronic stadiometer, Harpenden stadiometer, and the Raven Magnimetre, where techniques of measurement were similar, a wide range of observed SDs for the 10 children was nevertheless evident, ranging from approximately 0·1 to 0·4 cm. Analysis of the components of variance showed that the subjects' contribution to the total variance ranged from 100% (electronic stadiometer) to 88% (Minimetre), observers and instruments accounting for the remainder.

(3) REPRODUCIBILITY OF HEIGHT MEASUREMENTS —VARYING CONDITIONS

Table 3 shows the SDs obtained in a further

Table 2 Mean heights (cm) recorded by different observers

	Holtain electronic stadiometer	*Harpenden stadiometer*	*Raven Magnimetre*	*Raven Minimetre*	*Harpenden pocket stadiometer*
Observer X	130·10	129·76	130·06	129·99	129·94
Observer Y	130·28	130·09	130·27	129·91	129·99
Difference X-Y	−0·18	−0·33	−0·21	0·08	−0·05
p Value	0·027	0·00014	0·00012	0·19	0·76

Mean heights shown are for 10 children measured by two observers three times each on the five instruments.

Table 3 Reproducibility of height measurements (varying conditions)

	(i) *SD (cm)*	*(ii)* *SD (cm)*	*(iii)* *SD (cm)*
Harpenden stadiometer	0·36	0·22	0·11
Raven Magnimetre	0·21	0·19	0·16

SDs are based on measurements made under the following conditions (i) standard experimental—that is, blind and in random order, (ii) blind, successive, and (iii) non-blind, successive.

trial under the following three conditions: (i) standard experimental—that is, blind, randomised, (ii) blind, successive, and (iii) non-blind, successive. The SDs under standard conditions (i) were comparable with those obtained in the previous trial. The SDs were smaller however under conditions (ii) than (i), and further reduced under (iii), very clearly so as in the case of the Harpenden stadiometer.

Discussion

Our data should give rise to concern, whether in the community, hospital clinic, or research department. Correctly installed instruments have been shown to measure a metre rod or wooden block with good reproducibility. Screening for abnormal stature in the community, however, may be liable to serious inaccuracy through malpositioning of the measuring instruments. As the school entry medical is often the first and only time the height of a child is formally assessed, abnormally small children missed then might not be referred for a specialist opinion until a much later age, by which time the potential for modifying the final adult height may be greatly reduced. The installation of height measuring instruments can be easily and quickly checked with a metre rod at the beginning and end of each session. We have shown that, accurately installed and correctly used, an inexpensive Microtoise or Minimetre may be no less reliable than a more expensive instrument.

Where children are measured more than once in order to monitor their growth, reproducibility of height measurement is critical. Even under ideal conditions—that is, blind and randomised—the SD of a single height measurement was fairly constant, generally between 0·2 and 0·3 cm, the range previously observed by Tanner[13] and by the present authors in routine quality control checks.

Instruments themselves appear to contribute very little to the total variability and attempts to design still more sophisticated models may not be worth the effort. There may, of course, be an interaction between instrument and subject that is not apparent when only a wooden block is measured. For example, while the pocket stadiometer was reproducible when measuring the wooden block, it performed less well measuring a child, probably because the design incorporates no fixed horizontal or vertical parts.

Trained and experienced observers differ little among themselves in reproducibility of their measurements. We have shown, however, that differences in technique call for repeat measurements on individual children to be made not only with the same instrument, but also by the same observer. The difference in heights recorded by different observers also implies that either one or both of the observers is not measuring the 'true' height of the child, that is, the measurements are biased *or* there is no such thing as the true height of a child.

The greatest source of variablity was clearly the child himself. The ideal child to measure would be rigid. A living subject, however, is of no fixed height. Independently of diurnal variation, posture can vary from one moment to the next, and the aim of measurement can only be to estimate a child's mean height by making several separate observations.

The reproducibility of *individual* subjects on *individual* instruments varied considerably. Accordingly, statements of the error of measurement based on selected cases could be misleadingly low. It is of practical use to know how small the error *can* be. What is required, if there is no time to calibrate each individual child, is the best estimate of the likely error, given a child presumed to be 'average'. Hence the value of an 'estimated standard deviation', established for that particular combination of observer and instrument, as a clear and simple expression of error.

We have shown that the SDs of successive and non-blind observations tend to be lower than those obtained under standard experimental conditions, giving an estimate of the error that is artificially small. Even where children are repositioned and observations are blind, successive measurements, where no other children are measured between, underestimate the variability. Under such conditions, the observer is perhaps better able to replicate his technique, or the child to retain the same posture. Posture might be expected to change throughout the day in much the same way as, for example, the pulse rate. The pulse rate sampled randomly over a long period would have an accurate mean but large variance. Sampled over a short period, however, successive observations would have a smaller variance, but a mean that may not necessarily represent the 'usual' rate for the subject.

Our data point to the need for measurements to be not only random but blind as well. Where the observer is aware of the first measurement, he may consciously or otherwise try to make the next and subsequent readings as close as possible. Only the first reading is unbiased; the others have distributions conditional on the first, and the smaller SDs obtained relate only to the internal variability between the correlated measurements, not to their scatter around the target or 'true' height.

A similar problem to this arose many years ago with the need for reliable, uncorrelated measurements of blood pressure in drug trials.[14] It was resolved by developing the random zero sphygmomanometer, an instrument with which clinicians are able to perform repeat 'blind' measurements unaided, as the previous reading is disguised. A random zero stadiometer would be a useful tool in auxology.

Non-blind and/or successive observations could explain some of the high reproducibility of measurement claimed by other authors. Accuracy, or closeness to the target (fig 1A) should be the goal, however, and should not be sacrificed for high reproducibility (fig 1B). If confidence intervals are to be attached to a height measurement, an estimate of the SD of the larger variance about the mean in fig 1A is needed, not the smaller internal variance in fig 1B.

CONCLUSIONS

(1) The measurement of height is seriously hampered by the inaccurate installation of measuring instruments. (2) Some error is inevitable in measuring the height of children, the child himself being the major source of variance. Even where a trained observer uses an accurate and reproducible instrument, this error persists and the estimated SD is remarkably constant, generally in the region of 0·2 to 0·3 cm for a single height measurement. (3) Smaller reported errors could arise through failure to observe standard experimental conditions, or the reporting only of selected cases.

RECOMMENDATIONS

(1) Height measuring instruments should be regularly checked with a metre rod to ensure they are accurately set up. (2) All personnel concerned with the measurement of height should establish their own SD for a single height measurement, using their own instruments and a representative sample of subjects in a 'blind' and randomised calibration trial. (3) The monitoring of height should be carried out by the same observer using the same instrument. Ideally, several blind and non-successive measurements should be made by, for example, measuring several other children in between. (Under these stringent conditions, and only then, can the SD of a single height measurement be reduced by root n, where n is the number of measurements made.) (4) Studies relating to growth should routinely include the error of measurement of the individual researcher or researchers involved in the study. Where this is omitted, the published data cannot be evaluated. (5) We believe that the 'estimated standard deviation' provides a clear and simple expression of reproducibility, and propose that it should be routinely adopted.

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Are measurements of height made by health visitors sufficiently accurate for routine screening of growth?

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Abstract

To find out whether measurements of height made by health visitors are sufficiently accurate for use in routine screening of children we carried out an interobserver and intraobserver reliability study. Height measurements were made on a group of 10 children aged 3 years old and 10 aged 4·5 years old by two sets of four health visitors. They used a Microtoise or wall chart and the measurements were compared with those made by a trained auxologist with a Harpenden stadiometer. For a single assessment of height both pieces of equipment gave reasonably accurate results. In a child aged 3 years, with height measured on the Microtoise as 100 cm, the true height could be expected—with 95% probability—to lie between 99·2 cm–101·8 cm. At the age of 4·5 years, if the measurement was 110 cm, the child's true height could be expected to lie between 108·9 cm and 111·9 cm. The narrowest confidence interval for the growth rate from 3 to 4·5 years was achieved with the Microtoise, taking the mean of three measurements.

We conclude that measurements made by health visitors are sufficiently accurate for routine screening of height, and the use of such measurements for the calculation of height velocity could be improved by more structured training.

It is essential to detect children with short stature and abnormally slow growth as early as possible so that problems that are amenable to treatment, such as growth hormone insufficiency, can be treated. In a recent national review of the child health surveillance programme it was recommended that all children should be screened for growth at 3 and 4·5 years.[1]

The Oxford wall chart (devised by Aynsley-Green and Macfarlane) provides a simple approach to population-screening for short stature that can be used by health workers with only simple basic training.[2] Screening to detect young children whose height lies more than 2 SDs below the mean height for age, however, may not detect all of those with growth hormone insufficiency.[3] Early detection of these children requires an accurate assessment of growth velocity as the stature of these children may not have fallen outside the normal range by the age of 4·5 years.

Effective screening should therefore include both the measurement of height and an estimate of growth velocity, the calculation of which is dependent on two measurements. The accuracy of these measurements is therefore critical if the rate of false positive and false negative results is to be minimised.

Any national growth screening programme will have to rely on a primary health care team with little training in measuring techniques. Measurements undertaken as part of research protocols are usually made on sophisticated and often expensive pieces of apparatus, whereas measuring equipment provided for screening of the general population has to be simple and cheap.

To find out if measurements made by health visitors are sufficiently accurate for routine screening we undertook a study to examine the precision and accuracy of measurements made by health visitors with two simple pieces of equipment. Children at the ages of 3 and 4·5 years were measured and the results compared with those obtained by a trained auxologist with the standard equipment of a growth clinic: the Harpenden stadiometer.

Subjects and methods

The studies were carried out in the Oxford district with the approval of the local ethics committee. Ten 3 year old children and 10 aged 4·5 years old were recruited at random from a day nursery in Banbury. Two separate sets of four health visitors (one set for each age group) were given a brief period of instruction in the use of the Oxford Growth Screening Wall Chart (Castlemead Publications) and the Microtoise (Child Growth Foundation). They were then asked to make three separate measurements of each child with each piece of equipment. The children were measured in random order so that no child was measured by the same health visitor on consecutive occasions, and no health visitor had reference to previous measurements. Measurements made by the health visitors were then compared with those made by a trained auxologist (MLA) on a portable Harpenden stadiometer.

For the purpose of this analysis the stadiometer reading was assumed to be the correct height of the child. The accuracy of a measurement using any other method was therefore represented by the difference between this measurement and the stadiometer reading. In the analysis all the calculations were carried out on these differences, or biases. To see if there was any advantage in measuring each child three times and taking the mean value the analysis was carried out twice, firstly with the first

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measurement alone, and secondly with the mean of the three measurements.

To estimate the precision of the measurements (that is, the extent to which measurement biases differed from one another) an analysis of variance was carried out, assuming a random effects model. In this model both the observers and the children are considered as randomly chosen and thus as representing particular sources of variation. The total variance attached to a single measurement bias was taken as the sum of the variances due to observers, to children, and to random error (including any interaction between observers and children).[4] No allowance was made in the analysis for the sampling error of the variance estimates themselves.

Results

The mean (SD) of the measurement biases for the 10 children by age and method of measurement are shown in table 1. The negative mean values show the tendency of both methods to record a height that was lower than the true (stadiometer) value. The accuracy of different observers varied widely. For instance, with the 3 year old children using one reading on the Microtoise, the mean bias ranged from −0·10 cm for the most accurate observer to −1·01 cm for the least accurate. With the 4·5 year old children the corresponding range was from −0·06 cm to −1·17 cm.

The results for the 4·5 year old children show that the mean of three readings was slightly more accurate (that is, the mean bias was smaller) than the first reading alone. This was true for both the Microtoise and the wall chart. The opposite tendency was seen for the 3 year old children.

Table 1 Mean (SD) of measurement biases (cm) using the pooled results from all four health visitors

	Microtoise		*Wall chart*	
	3 years	*4·5 years*	*3 years*	*4·5 years*
One reading:	−0·48 (0·55)	−0·37 (0·54)	−0·27 (0·56)	−0·24 (0·57)
Three readings:	−0·58 (0·50)	−0·22 (0·36)	−0·46 (0·46)	−0·07 (0·43)

Results from the analysis of variance are shown in table 2. The components of variance (the variance attributed to each factor) show that for the 3 year old children the total variance was similar for both methods, but for the 4·5 year olds the mean of three readings using the Microtoise had the smallest total variance. For 3 year olds the proportion of total variance attributed to the children (between 29% and 51% of the total) was similar to the proportion attributed to the observers. In contrast, with the 4·5 year old children the proportion of the total variance attributed to the children (between 3% and 13%) was much smaller than that attributed to the observers.

The best estimate of the true height of a child is given by the measured height, with allowance made for the bias attached to the method of measurement used. The expected bias is the pooled mean from table 1. Assuming a normal distribution, 95% of all biases would be expected to lie within 1·96 SD of the mean (values given in table 2). So if a value of 100·00 cm were recorded for the 3 year old child using one reading on the Microtoise, the interval (100·00+0·48 (1·30)) cm that is 99·2 cm to 101·8 cm) would be expected—with 95% probability—to include the true height of the child. If, using the same method, the child's height at 4·5 years were recorded as 110·00 cm, the 95% confidence interval for the true height would be (110+0·37 (1·52)) cm—that is, 108·9 to 111·9 cm.

If the same children were measured on both occasions, the 95% confidence interval for the 18 month growth would be 7·9 cm to 11·9 cm (10·00+(0·37−0·48) (2·00) cm)—that is, a growth velocity ranging between 5·3 and 7·9 cm/year (table 3 and figure). The reported growth rate would be 10 cm in 18 months—that is, 6·7 cm/year.

Our results suggest that the most precise esimate of growth would be achieved using the Microtoise, and taking the mean of three measurements. For instance, with three readings on the Microtoise the band described above (7·9 cm to 11·9 cm) would be narrowed to between 8·1 cm and 11·2 cm.

Discussion

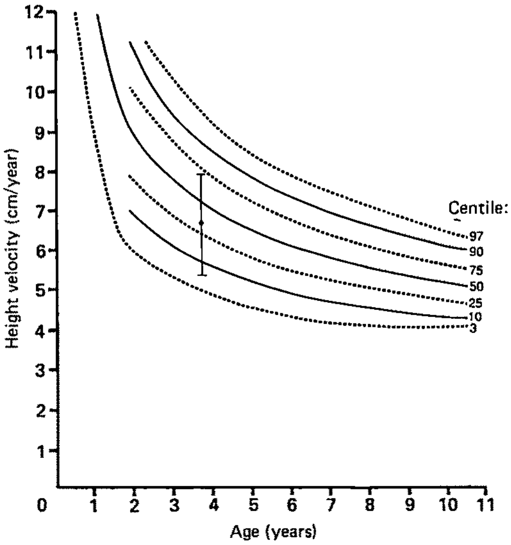
The conceptual and practical problems raised

Table 2 Components of variance of measurement biases (cm)

	Observers	*Children*	*Error*	*Total variance*	*1·96 SD*	*95% Confidence interval for bias*
Microtoise						
At 3 years of age						
One reading:	0·14	0·13	0·17	0·44	1·30	−1·78 to 0·82
Mean of three readings:	0·10	0·18	0·07	0·35	1·16	−1·74 to 0·58
At 4·5 years of age						
One reading:	0·31	0·03	0·27	0·60	1·52	−1·89 to 1·15
Mean of three readings:	0·17	0·01	0·12	0·30	1·08	−1·30 to 0·86
Wallchart						
At 3 years of age						
One reading:	0·18	0·14	0·17	0·49	1·37	−1·64 to 1·10
Mean of three readings:	0·18	0·14	0·07	0·39	1·22	−1·68 to 0·76
At 4·5 years of age						
One reading:	0·37	0·09	0·24	0·70	1·64	−1·88 to 1·40
Mean of three readings:	0·48	0·07	0·12	0·67	1·60	−1·67 to 1·53

Table 3 Variance of measurement biases (cm): growth from 3 to 4·5 years

	Total variance	*1·96 SD*	*95% Confidence interval for bias*
Microtoise:			
One reading	1·04	2·00	−1·89 to 2·11
Mean of three readings	0·65	1·58	−1·22 to 1·94
Wall chart:			
One reading	1·19	2·14	−2·11 to 2·17
Mean of three readings	1·06	2·02	−1·63 to 2·41



Height velocity standards of British boys.[8] The vertical line at 3·75 years shows the 95% confidence interval of 5·3 to 7·9 cm/year if the growth rate is 6·7 cm/year.

by errors of measurement are considerable.[5] The results of our studies have important implications for current recommendations for screening of growth during childhood. They show that different observers, with basic training but little experience in measuring techniques, may vary in the accuracy of their recorded measurements. Interestingly, all the observers tended to record heights lower than those observed by the trained auxologist. Standing height shows diurnal variation,[6] and the auxologist puts traction on the mastoid processes to decrease this.[7] The auxologist may also be more successful at getting children to stand upright. Our data show that further practice in measuring techniques clearly has an effect on the accuracy of measurements. With both pieces of equipment the accuracy of measurement by the health visitors was greater when the mean of three results in the 4·5 year old children were analysed. A screening programme for growth would mean that health visitors had to make multiple measurements, which may lead to improved techniques. There was no improvement in accuracy, however, when the means of three results in the 3 year olds were analysed.

Not all of the variance in the observed measurement biases could be attributed to the observers. A substantial part of the variance observed in the younger age group could be attributed to the children, and this is not surprising when one contemplates the problems of ensuring an erect and relaxed posture in a 3 year old child. Accurate measurements in this age group are often doubted by the best trained auxologists, and if children of this age or younger are to be screened the possibility of measuring length rather than height must be considered. Whereas measurements of height in 3 year olds may be difficult, weight is easy to determine accurately. Weight measurements do not, however, provide us with sufficient information for the assessment of linear growth. If a child's weight increases with time we only know that he had become heavier—but whether this is due to excess fat, increased bone or muscle, or retention of body fluid as a result of some pathological condition, is unknown.

The Oxford wall chart provides a simple and reasonably accurate way of measuring a child's height. Our results suggest however, that a more precise measure of height was achieved with the Microtoise taking a mean of three measurements. The Microtoise has now been replaced by the Minimetre (also available from the Child Growth Foundation) and this piece of apparatus rather than the wall chart should therefore be recommended for routine screening.

The accuracy and precision of measurements made by primary health care workers will ultimately determine the value and efficacy of growth screening. For example, from a recorded height of 100·00 cm in a 3 year old child, one could predict with the Microtoise that the child's true height would lie between 99·2 and 101·8 cm. This range is acceptable in screening for children with short stature but is it sufficiently accurate for the calculation of poor growth velocity? With the same methods, and by necessity with different observers, if the child's height at 4·5 years were recorded as 110 cm, the true growth over this period would be expected to lie between 5·3 and 7·9 cm/year.

The reported growth rate in this child would be just above the 25th centile for velocity as reported by Tanner *et al.*[8] [9] The true growth rate, however, might lie anywhere between the sixth and the 72nd centile on the velocity charts. Clearly a definition of normal growth based on these centiles will produce a large number of false positive values on screening for short stature. These problems may be further compounded by short intervals between measurements, which do not allow for seasonal variations in growth,[10] and the recently reported cyclical pattern of growth.[11] If the recommended criterion of the 25th centile for velocity as the cut off point for further investigation is adopted, errors in measurement will produce a large number of false positive results.[3]

Our results indicate that more training would improve the accuracy of measurements made by health visitors. Basic auxological training in both accurate measurement and interpretation of growth data must therefore be included in both health visitors' basic training and their 'in-service training'. Local training schemes for other primary health carers (including general practitioners) should also be considered before national growth screening can be undertaken.

We would recommended the validation of screening programmes within selected health districts with understanding of the problems of measurement and the interpretation of data before national screening is carried out.

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Psychological characteristics of children with Shwachman syndrome

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Abstract

Twelve children and young adults with Shwachman syndrome were compared with their unaffected siblings and with controls suffering from cystic fibrosis in terms of intellectual ability, motor skills, and behaviour. There were highly significant differences in intelligence quotient between those with Shwachman syndrome and the other two groups. Four of the index subjects but none of the control subjects were below the normal range. The differences between groups on other tests of cognitive and motor skills were not significant, though those with Shwachman syndrome tended to have the lowest scores. There was no evidence that those with Shwachman syndrome had more behavioural difficulties than the control subjects. We suggest that the intellectual difficulties of patients with Shwachman syndrome may be of neurological rather than social origin and that they may originate before birth.

Shwachman syndrome is a rare multiorgan disease of unknown cause first described in the 1960s.[1 2] In infancy the condition presents with failure to thrive, bulky offensive stools as a result of pancreatic exocrine insufficiency, intermittent thrombocytopenia and neutropenia, and growth and bone abnormalities (metaphyseal dyschondroplasia). Shwachman syndrome is the second most common cause of pancreatic insufficiency in well nourished North American and European children, with an incidence of 1:200 000,[3] and a possible autosomal recessive mode of inheritance.[4]

Symptomatic treatment with pancreatic enzymes and a low fat diet alleviates the problem of maldigestion, but poor growth often persists. Most patients remain below the third centile for height and weight into adult life[4] and administration of growth hormone does not improve growth.[5] Some early studies reported that affected children have adequate psychological development with normal motor milestones and mental abilities within the reference range.[1] Others reported that patients were occasionally grossly retarded (one child of four described by Shmerling *et al*[5] and two of 20 described by Bodian *et al*[2]), and one mentioned more subtle developmental delays (in milestones and intelligence quotient (IQ)).[4] The psychological characteristics of children with Shwachman syndrome, however, have not been studied systematically.

In this study we have examined intellectual ability and achievement in a group of 12 children and young adults with Shwachman syndrome. We compared them with their unaffected siblings (who share the family environment but not the disease) and with matched controls with cystic fibrosis (who share many similarities in illness and hospital treatment, but not family environment).

Subjects and methods

All children and young adults with Shwachman syndrome who were between 4 and 20 years old at the time of the study and who had been diagnosed or treated, or both, at the Hospital for Sick Children were invited to enter the study. Many had also been included in the study by Aggett *et al.*[4] Seventeen children were identified but one had died, the parents of two refused (in one case because they thought that the diagnosis was incorrect), and two were lost to follow up, leaving a possible 12 children. At the time of the study, one of these 12 was too ill to take part, but a further child was identified in Birmingham whose family agreed to participate, making 12 children in all. Eight of the 12 children also had unaffected siblings who agreed to take part for comparison (table). When there were several unaffected siblings, the one nearest in age was asked to participate in the study.

A second control group, of children matched for age, sex, and social class, was selected from the London register of children with cystic fibrosis. All those approached agreed to participate.

PROCEDURE

Index and control subjects were normally assessed at the hospital that they usually attended, on the same day as their routine outpatient appointment. Siblings were asked to accompany the affected child and were tested on the same day. One subject no longer attended hospital and was seen in the local health centre instead.

On assessment the parents were interviewed to provide developmental, social, and medical details (for example, developmental milestones, time off school because of illness, and peer relationships) and the Connors parent questionnaire was administered.[6] Subjects and controls were given age appropriate IQ tests (McCarthy scales of children's abilities; Wechsler preschool and primary scale of intelligence; Wechsler intelligence scale for children, revised edition; and Wechsler adult intelligence scale, revised edition). They also completed the Annett and Kilshaw pegboard (a test of manual motor skill)[7]; an immmediate and delayed visual recall mem-

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Age, sex, and IQ of patients with Shwachman syndrome, control subjects (siblings), and control subjects with cystic fibrosis

Patients with Shwachman syndrome				*Sibling control subjects*			*Control subjects with cystic fibrosis*		
Case No	*Sex*	*Age (years)*	*IQ*	*Sex*	*Age (years)*	*IQ*	*Sex*	*Age (years)*	*IQ*
1	Male	3·9	(48)	Female	6·4	106	Male	4·7	132
2	Female	4·8	76	No sibling			Female	5·08	114
3	Female	4·8	105	Male	8·5	125	Female	5·08	119
4	Male	10·3	105	No sibling			Male	11·4	116
5	Female	12·3	68	Male	9·3	102	Female	12·3	88
6	Female	13·3	69	Male	11·0	90	Female	14·2	80
7	Female	14·08	61	Male	11·7	92	Female	14·8	92
8	Male	15·3	88	No sibling			Male	15·3	112
9	Female	18·2	76	Female	20·08	99	Female	17·5	90
10	Female	18·7	90	No sibling			Female	18·6	96
11	Female	19·9	71	Female	13·0	91	Female	20·0	93
12	Female	11·0	82	Male	8·2	113	None available		
Mean (SD)		12·5 (5·5)	81 (14·6)*		11·0 (4·2)	102·3 (12·2)		12·6 (5·5)	102·9 (16·3)

*Excluding case 1.
Case 8 and case 10 were siblings.

ory test from the British ability scales[8]; a test of visuomotor skill (the Bender-Gestalt test of visuomotor development)[9]; the Bruininks-Oseretsky motor skills test,[10] and a word reading test from the British ability scales.[8] The large age range meant that not all these tests were suitable for all subjects; numbers of subjects reported as completing the tests in the results section therefore vary accordingly.

Statistical analysis was by the Student's paired *t* test using two tailed probability estimates.

The children and young adults with Shwachman syndrome were exactly matched for sex and social class with those with cystic fibrosis (four were social class I or II, and the remaining eight were social class III). The mean (SD) ages for the two groups were similar, being 12·5 (5·5) years and 12·6 (5·5) years, respectively. Three of the siblings of the patients with Shwachman syndrome were older than the affected children, and five were younger (mean age of siblings 11·0 years); two sibling pairs were girls, but the other siblings were opposite sexes to the affected children (three girls and five boys altogether).

Results

PSYCHOMETRIC TESTS

The results are shown in the table. One child (case 1) was severely handicapped and could not achieve a score on the appropriate IQ test. He was therefore assessed on the Griffiths's mental development scale.[11] His developmental quotient is given in parentheses in the table as this scale has a different mean (SD) from the other scales and his developmental quotient was not included in the statistical analysis. Patients with Shwachman syndrome had significantly lower IQs than their siblings, differences ranging from 20 to 34 (mean 25·7) $t=11·25$, df 6, $p<0·0002$ (excluding case 1) and the control patients with cystic fibrosis (differences ranged from 6 to 38 points (mean 19·1) $t=6·08$, df 9, $p<0·0005$) (excluding case 1). The control patients with cystic fibrosis, however, did not differ from the siblings in IQ ($t=0·31$, df 6, $p>0·05$). No particular pattern of deficits was found among the subtest scores of the patients with Shwachman syndrome.

In terms of motor skills (for those who were able to complete the Annett pegboard) those with Shwachman syndrome were slower than their siblings but faster than those with cystic fibrosis as measured by z scores. This was true for both right and left hands but none of the differences was significant. Only five with Shwachman syndrome, four with cystic fibrosis and five siblings completed the Bruininks-Oseretsky test of motor development (age range 4 to 14 years). The results showed that although those with Shwachman syndrome did less well than their siblings ($t=1·85$, df 4) and those with cystic fibrosis ($t=2·17$, df 3), these differences did not reach significance, perhaps because of the small numbers studied. The scores on the Bruininks-Oseretsky test and the IQ test were strongly positively correlated (Pearson $r=0·73$, df 12, $p<0·002$), as might be expected.

The results of the British ability scales visual memory test showed that the patients with Shwachman syndrome scored less well (in terms of T scores) than their siblings on both immediate and delayed memory, but the index cases and those with cystic fibrosis had similar scores for both immediate and delayed recall. None of the differences in memory testing were significant. The group with Shwachman syndrome also made more errors on the Bender-Gestalt test (using the Koppitz scoring system) than those with cystic fibrosis, though this did not reach significance on a paired *t* test ($t=2·29$, df=6, $p=0·06$).The scores of the group with Shwachman syndrome on the Bender-Gestalt test could not be compared with those of their siblings because of the age differences (error scores on the Bender-Gestalt test are age related).

Finally, comparison of the subject's reading skills (by T scores) on the British ability scales word reading test indicated that those with Shwachman syndrome were doing only a little less well than their siblings and the cystic fibrosis controls, and none of the differences were significant.

INTERVIEW WITH THE PARENTS

Interviews with the parents suggested that in terms of early history the largest difference between the groups was that of birth weight. All but one of the children with Shwachman syndrome were lighter at birth than their siblings (the exception was a sibling who had been born prematurely), and this difference was significant by the paired *t* test ($t=2 \cdot 91$, df 7, $p=0 \cdot 02$). The children with Shwachman syndrome were also significantly lighter at birth than those with cystic fibrosis (paired *t* test, $t=2 \cdot 89$, df 10, $p<0 \cdot 02$); those with cystic fibrosis did not differ from the siblings ($t=0 \cdot 25$, df 6, $p=0 \cdot 8$).

There was some indication of delayed speech and motor milestones among the children with Shwachman syndrome. For instance, four of them had not sat up unsupported until they were more than 9 months old, according to their parents, whereas none of the other children had started sitting so late. The age of walking did not differ across the groups. Five of the children with Shwachman syndrome said their first words after 12 months of age, whereas only one other child started talking so late. In view of the age of some of the other subjects, however, and the effect this may have on the accuracy of parental recall the milestone data have to be treated with caution.

Children's scores on the Connors parent questionnaire varied greatly in all groups and the differences between groups did not approach significance. In terms of absences from school, parents of children of school age with Shwachman syndrome reported that some had had more than a week off school during the previous three months. Two children and one young adult were off work for this time. Children and young adults with cystic fibrosis had rather more time off on the whole (four had had more than two weeks off, and three had had one to two weeks off school or work). Siblings of the children with Shwachman syndrome had also sometimes had more than one week off school or work (n=3), suggesting that in general those with Shwachman syndrome were not missing undue amounts of schooling when compared with their siblings, and were missing less schooling than children with cystic fibrosis.

Discussion

The mean IQ for the children and young adults with Shwachman syndrome was more than one standard deviation below the mean for the general population and was significantly lower than the mean IQ of both their siblings and matched controls with cystic fibrosis. Four of those with Shwachman syndrome scored less than 70 for full scale IQ and this fell below the accepted reference range (that is, more than two standard deviations below the mean of the general population). One of the four fell into the range of severe learning difficulties (case 1). None of the siblings and none of the patients with cystic fibrosis scored outside the normal range, and the mean IQ of the two control groups was close to the mean for the general population.

Other psychometric tests almost always showed poorer performance by children and young adults with Shwachman syndrome when compared with siblings and with those with cystic fibrosis. The restricted age ranges of many of the tests meant that the numbers in each group were sometimes small, and none of the differences were significant. The poorer motor skills of those with Shwachman syndrome may have been a function of IQ and this kind of general correlation of test scores with IQ may also have accounted for other differences in test results among groups.

There are a number of reasons why children and young adults with Shwachman syndrome may be less able than their siblings and than those with cystic fibrosis. Firstly, it could be argued that when children have a chronic illness they will inevitably miss some schooling and this, together with the stress associated with the illness, may depress their scores on psychometric tests. If this is the case, it would be predicted that children with Shwachman syndrome would score as well as those with cystic fibrosis (or even better, given our evidence of rather more time off school for those with cystic fibrosis). The children with cystic fibrosis were doing better than those with Shwachman syndrome, however, though admittedly the two group's scores were most alike for 'attainment' tests, such as reading. Thus absence from school cannot explain the findings on IQ.

Secondly, it might be that the small size of the children with Shwachman syndrome meant that they were treated as much younger children, thus retarding their emotional and cognitive development.[12] Again, children with cystic fibrosis would be expected to be similarly affected, as their growth is also poor. This explanation, therefore, is also inappropriate.

Finally, it may be that in Shwachman syndrome there is some subtle neurological damage that does not occur in cystic fibrosis. This explanation fits the findings of the study best, as it would follow from this that there would be significant differences between the children with Shwachman syndrome and their siblings and between those with Shwachman syndrome and those with cystic fibrosis, but no differences between those with cystic fibrosis and the unaffected sibling group. Moreover, it would be expected that measures of intellectual potential would be more affected than attainment, as was indeed the case. There was no evidence of an increasing deficit with increasing age in this study for those with Shwachman syndrome, though whether the children's IQ declines over time can only be answered satisfactorily by a prospective longitudinal study. It is possible that any neurological damage may occur within the uterus, however, and this would not necessarily increase after birth. The significant differences between the children with Shwachman syndrome and the other groups in birth weight suggests that prenatal adversity may well be an important factor.

The reasons for intellectual difficulties in children with Shwachman syndrome will probably remain unclear for some years. It is now certain, however, that these children should be considered at risk of developmental delay and early intervention programmes should be made available to them.

We are grateful to all the children, young adults, and parents who took part in the study. We also thank the many paediatricians who allowed us access to index and control cases.

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Increase in serum concentrations of IgG_2 and IgG_4 by selenium supplementation in children with Down's syndrome

G Annerén, C G M Magnusson, S L Nordvall

Abstract

In a previous study on children with Down's syndrome a reduced rate of infections was reported by their parents after the children had received six months' treatment with selenium supplements. In the present study the concentrations of the four IgG subclasses were measured in 29 of these children in samples of serum obtained before and immediately after the period of supplementation and one year after it had finished. Selenium had a significant augmentative effect on the serum concentrations of IgG_2 and IgG_4, but not of IgG_1 and IgG_3. This effect was not related to age, as among children over the age of 6 years the serum concentrations of IgG_2 and IgG_4 had decreased significantly one year after the treatment had been stopped. This study suggests that selenium has an immunoregulatory effect, which might be of importance in both basic research and clinical practice.

Susceptibility to infections is a feature of Down's syndrome and is likely to be caused by abnormalities in host defence—for example, in the immune response.[1] In patients with Down's syndrome the serum concentration of IgG is either normal or slightly raised.[1] The serum concentrations of the IgG_2 and IgG_4 subclasses are significantly reduced, and those of IgG_1 and IgG_3 are normal or increased in both adults[2] and children with Down's syndrome (G Annerén *et al*, unpublished observations). In a study of six months' selenium supplementation in children with Down's syndrome that was designed to investigate the effect on the activity of glutathione peroxidase in erythrocytes and on the concentrations of selenium in the plasma and erythrocytes, many of the parents spontaneously reported a reduced rate of infections among their children after treatment with selenium.[3]

Older patients with Down's syndrome tend to develop a presenile dementia that has striking similarities to Alzheimer's disease. It has been suggested that this might be due to increased lipid peroxidation as a secondary gene dosage effect of the 50% increase in the activity of superoxide dismutase in trisomy 21 cells. The rationale for selenium supplementation was to find out whether the activity of the selenium dependent enzyme glutathione peroxidase would increase and improve the protection against oxygen radicals.[3]

The aim of the present study was to investigate whether the reported decrease in infections could be related to a change in the serum pattern of IgG subclasses among children with Down's syndrome.

Patients and methods

In the previous study 48 children with Down's syndrome, verified by chromosomal analysis, who were living at home were enrolled.[3] Selenium was given as selenium rich yeast tablets (Novamed Selen, Huhtamäki OY) in a dose of 10 μg/kg body weight/day for six months. The children were examined clinically before and immediately after the six month supplementation period, and again one year later. On each of these three occasions a sample of serum was collected and stored at −20°C until it was analysed. The plasma and erythrocyte selenium concentrations increased roughly fourfold during the period of supplementation and had almost regained the pretreatment concentrations one year after withdrawal.[3] Sufficient volumes of serum for the present study were available from 29 of the 48 children: 19 boys and 10 girls, aged 1·5 to 15 years.

The serum concentrations of the four subclasses of IgG were determined by a competitive two step microtitre enzyme linked immunosorbent assay (ELISA) based on subclass specific monoclonal antibodies and rabbit antimouse immunoglobulin antibodies conjugated to alkaline phosphatase. The assay conditions regarding the buffers used, incubation times, sample dilutions and the evaluation of specificity, sensitivity, linearity, precision and accuracy will be described in detail elsewhere (CG M Magnusson, unpublished observations). All three serum samples from each patient were assayed in duplicate on the same plate to minimise intrasubject variations. A commercial standard serum (H00–03, Janssen, Belgium), calibrated against the World Health Organisation 67/97 standard,[4] was used to produce standard curves. Interassay imprecision, which was evaluated by including two dilutions of a control serum on each plate, gave coefficients of variation on seven different plates of 4·9% for IgG_1, 5·8% for IgG_2, 5·1% for IgG_3, and 8·9% for IgG_4. Undetectable IgG_4 (<5 mg/l) was assigned a value of 2·5 mg/l.

Statistical analysis was by Wilcoxon's signed rank test. Because of the age dependence of IgG subclass concentrations, the children were split into two age groups, ≤ 6 (n=13) and >6 years (n=16), for the statistical analyses.

Results

After a six month period of selenium supple-

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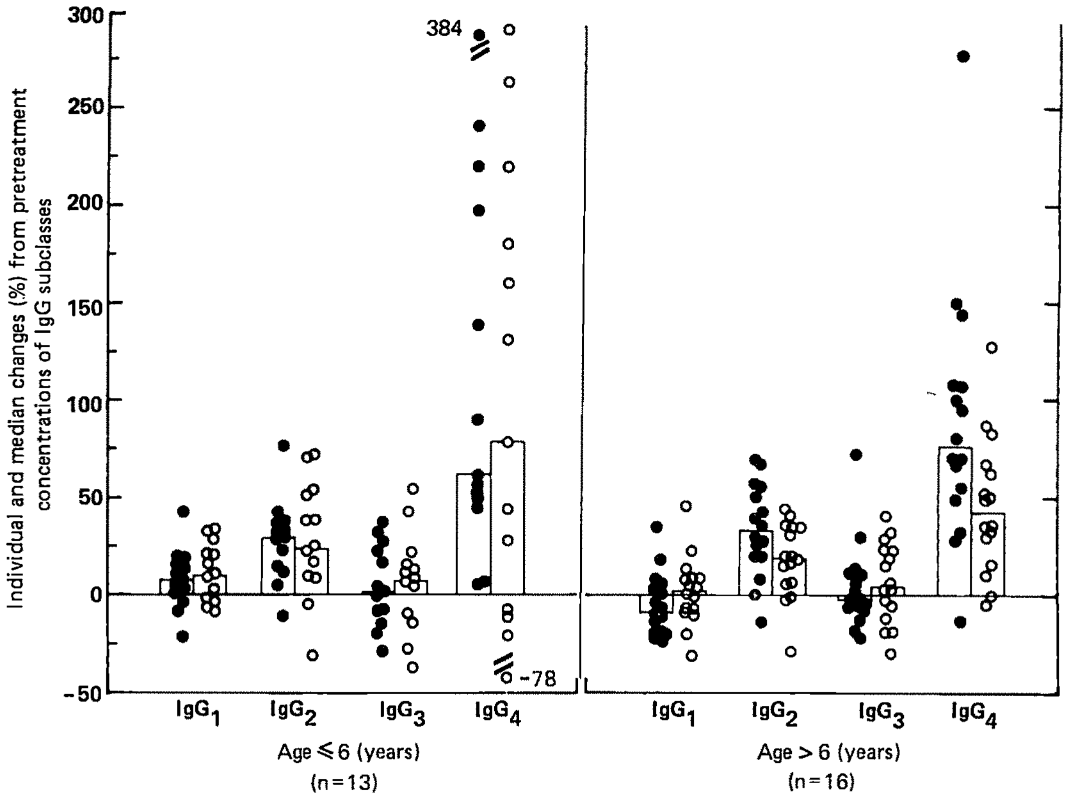

Individual and median percentage changes from pretreatment serum concentrations of the four IgG subclasses in 29 children with Down's syndrome, after a six month course of selenium supplementation (●) and one year after withdrawal of the supplementation (○). The histograms indicate the median percentage changes.

Mean IgG subclass serum concentrations (g/l) in 29 children with Down's syndrome before (0) and after a six month course of selenium supplementation (6), and 12 months after withdrawal of the selenium supplementation (18).

Group	*Sample time (months)*	*Immunoglobulin subclass*			
		IgG_1	*IgG_2*	*IgG_3*	*IgG_4*
Age ≤6 years (n=13)	0	7·55	0·76	0·56	0·016
	6	8·11	0·97	0·57	0·031
	18	8·36	0·96	0·58	0·025
Age >6 years (n=16)	0	10·7	1·21	0·72	0·048
	6	10·1	1·59	0·74	0·087
	18	10·8	1·41	0·75	0·069

mentation the serum concentrations of IgG_2 and IgG_4 were significantly increased in both the younger and the older children (figure). The median increase in IgG_2 was 30% ($p<0·005$) in the younger age group and 33% ($p<0·001$) in the older group. The corresponding median increases in IgG_4 were 61% ($p<0·005$) and 75% ($p<0·0005$). The IgG_2 ($p<0·05$) and IgG_4 ($p<0·005$) concentrations had declined significantly in the older age group (>6 years of age) one year after the stopping of selenium, but were essentially unchanged in the younger age group. In contrast, the serum concentrations of IgG_1 and IgG_3 were not significantly affected by selenium supplementation in either age group.

Discussion

In this study selenium supplementation was found to have an augmentative effect on the serum concentrations of IgG_2 and IgG_4 in children with Down's syndrome, which is of particular interest because concentrations of these two subclasses are low in patients with Down's syndrome (G Annerén *et al*, unpublished observations).[2] Although no control group was included the data seem convincing because both the IgG_2 and IgG_4 concentrations declined significantly during the year after withdrawal of supplementation among children >6 years. A corresponding decrease in the younger age group was probably masked by an expected rise in these subclasses with age.[5] To our knowledge this is the first study showing a linkage between selenium treatment and immunological host defence in man.

Children with Down's syndrome are especially prone to respiratory bacterial infections.[1] This may be partly explained by a deficiency in IgG_4,[6] and IgG_2 antibodies, of which the latter are known to be directed against bacterial polysaccharide antigens of encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae.*[7] The effect of selenium serum IgG_2 and IgG_4 concentrations may therefore be of clinical importance and in some way related to the spontaneously reported reduced rate of infections among the children with Down's syndrome. We are unable to present trustworthy clinical correlates to our laboratory data, however, as the original study was not designed for this purpose. It also remains to be investigated whether the observed effects upon IgG_2 and IgG_4 are confined to patients with Down's syndrome alone.

Our limited knowledge about the biological role of selenium is partly because selenium deficiency is uncommon. In Keshan disease, an endemic cardiomyopathy afflicting Chinese children, there is a protein deficiency that coexists with selenium deficiency, making it difficult to decide which symptoms are the result of the selenium deficiency.[8] From animal experiments and veterinary medicine, however, selenium supplementation is known to be beneficial for host defence.[9] Although in a few studies in man selenium has been found to have no or only slight effects on granulocyte and lymphocyte function,[10] low selenium concentrations have been found among patients with severe bacterial infections, but not in those suffering from viral infections.[11] Our results confirm these data, in view of the fact that it is mainly IgG_2 that plays a part in the immune response to bacterial antigens,[7] while viral infections trigger mainly IgG_1 and IgG_3 responses.[12] Thus with a low dietary intake of selenium there seem to be grounds for suspecting that there is a vicious circle comprising selenium deficiency, reduced serum IgG_2, and repeated infections.

The results of the present study were unexpected and no explanation of the mechanisms of action can be offered. Further studies are under way to elucidate the immunoregulatory effect of selenium and to find out if it can be of any clinical value in the management of infection prone children, with or without Down's syndrome.

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Late deaths after treatment for childhood cancer

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Abstract

An investigation of 749 deaths occurring among 4082 patients surviving at least five years after the diagnosis of childhood cancer in Britain before 1971 has been undertaken. Of the 738 with sufficient information the numbers of deaths attributable to the following causes were: recurrent tumour, 550 (74%), a second primary tumour, 61 (8%), a medical condition related to treatment of the tumour, 49 (7%), an traumatic death unrelated to the tumour or its treatment, 34 (5%), finally, any other cause unrelated to the tumour or its treatment, 44 (6%).

Less than 10% of five year survivors of non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilms' tumour, or a soft tissue sarcoma died of recurrent tumour during the next 15 years, while more than 25% of five year survivors of Hodgkin's disease, ependymoma, medulloblastoma, and Ewing's tumour died of recurrent tumour during the corresponding period. Almost 50% of five year survivors of acute lymphoblastic leukaemia died of recurrent disease during the corresponding 15 years, a large proportion of deaths being due to central nervous system relapse in an era before central nervous system prophylaxis was routinely given.

Comparison of the mortality observed with that expected from mortality rates in the general population indicated three times the expected number of deaths from non-neoplastic causes. Five times the expected number of deaths from cardiovascular causes were observed, these were predominantly myocardial infarction and cerebrovascular accidents. There was no evidence of an excess in the number of suicides observed, but there were three times the expected number of deaths from accidents observed after central nervous system tumours.

Two groups of patients were identified whose deaths were potentially avoidable. Seven patients with craniopharyngioma and panhypopituitarism presented with addisonian crises during periods of stress not adequately covered by exogenous corticosteroids. In the other group were children who received radiotherapy and later developed problems related to radiation fibrosis.

We emphasise that our investigation relates to patients diagnosed with childhood cancer before 1971. The pattern of mortality that will emerge after recent treatment regimens, in which chemotherapy is being used more extensively, is likely to be different from that observed in our study.

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Examination of the course of events leading to death among patients who survive at least five years after childhood cancer is important as it may provide further understanding of late relapse and the late effects of treatment. With the benefit of hindsight it may be possible to identify deaths that might have been preventable. If the study population is large it is likely that deaths from rare adverse consequences of the neoplastic disease or its treatment will be identified. Such an investigation requires clinical information relating to the circumstances of death and therefore access to sources other than the death certificates, including hospital records and reports from postmortem examination.

A comparison of the mortality observed with that expected from mortality in the general population, for specific causes of death—both neoplastic and non-neoplastic—may also provide further insight into the curability of childhood neoplastic disease and identify any departure from the expected pattern of mortality. For this type of comparison it is necessary to rely on death certification because the expected numbers are derived from general population rates which are themselves based on death certificates alone.

This paper is complementary to our previous report on long term survival and cure after childhood cancer.[1]

Methods

The national register for childhood tumours, maintained by the Childhood Cancer Research Group in Oxford, has been routinely notified of tumours occurring in children under 15 years of age since 1962 through the national cancer registration scheme operating in Great Britain. This provides, within the limits of completeness of registration, a population based series of childhood cancer cases. From among these we have selected 2537 cases diagnosed before 1971 who survived for at least five years. A further 1545 cases, diagnosed between 1940 and 1961 inclusive, surviving at least five years, and treated at centres where complete lists of patients were available, have also been included.

A consequence of restricting the study to this period of diagnosis is that we are primarily concerned with malignant disease that was amenable to treatment with radiation and surgery, as apart from the treatment of leukaemia, cytotoxics were not in widespread use before 1971. An advantage of studying this period, however, is that sufficient time has elapsed to examine late mortality.

For deaths occurring five or more years from diagnosis, an effort was made to obtain medical details of the circumstances leading to death. A complete copy of all relevant hospital notes extant was obtained together with a copy of the report when a postmortem examination had been undertaken.

The underlying cause of death, based on all the information available, was coded according to the following broad categories: (1) recurrent tumour; (2) a medical condition related to treatment of the tumour; (3) a second primary tumour; (4) a traumatic death apparently unrelated to the tumour or its treatment; (5) any other cause apparently unrelated to the tumour or its treatment; and (6) insufficient information.

A few conventions were used in coding deaths into these broad categories. In patients with tumours of the central nervous system, the cause of death given on the death certificate was frequently bronchopneumonia. Examination of the case records of a number of these patients showed that their general health had gradually declined, the patients had become obtunded due to recurrent tumour and had eventually died from bronchopneumonia. These deaths were all coded as recurrent tumour rather than infection. When death occurred from infections such as herpes zoster, meningitis, or pneumonia in patients on chemotherapy then they were coded as a death from a medical condition related to treatment of the tumour. One patient with Hodgkin's disease who had undergone a splenectomy and had subsequently died from a pneumococcal septicaemia, while in remission, was also coded to a medical condition related to treatment. When death occurred from infection or other cause and where there was insufficient evidence to determine whether the patient had active disease at the time, then the death was coded to insufficient information.

For the purposes of comparing the mortality observed with that expected we also recorded the International Classification of Diseases (ICD) code appearing on the death certificate. We restricted the study to revisions 6, 7, 8, and 9 of ICD,[2–5] and therefore only deaths occurring after 1949 are included in this comparison. This excluded one death.

Survival was examined using standard techniques.[6] Mortality from specific causes of death among survivors was compared with that expected from the general population of England and Wales (Office of Population Censuses and Surveys, unpublished report). Observed and expected numbers of deaths were compared using exact Poisson methods.

Results

Of the 4082 five year survivors eligible for analysis, there were 749 deaths. A death certificate was obtained for 739 of these deaths, hospital notes for 359, and a postmortem examination report for 76.

Table 1 gives the causes of late death occurring among patients surviving for at least five years after diagnosis of various childhood neoplasms. There was insufficient information available to code the cause of death in 11 patients. Approximately 74% of the deaths were attributed to recurrent tumour, and 8% to the occurrence of a second primary tumour. There was substantial variability in the relative proportions of deaths from different causes depending on the primary diagnosis: over 75% of deaths after acute lymphoblastic leukaemia, lymphoma, and tumours of the central nervous system or bone were due to recurrent tumour. In contrast, only 26% of deaths among patients surviving at least five years after genetic retinoblastoma were due to recurrent tumour, with 65% resulting from second primary tumours. Similarly, among patients surviving at least five years after Wilms' tumour only 36% of deaths were due to recurrent tumour with 32% resulting from second primary tumours.

Table 2 gives the variation in causes of death with follow up. Among deaths occurring five to nine years from diagnosis recurrent tumour was the most common cause of death after each childhood neoplasm. The most common cause of death among 10 year survivors varied considerably depending on the neoplasm: in patients with acute lymphoblastic leukaemia, Hodgkin's disease, and central nervous system tumours, recurrent tumour was still the most common cause, whereas in patients with retinoblastoma and Wilms' tumour, death from second primary tumours predominated.

There were 188 deaths from causes other than recurrent tumour (table 1). Of these, we obtained hospital notes and/or a postmortem

Table 1 Frequency (%) of different causes of death observed among those surviving five or more years from diagnosis

	Acute lymphoblastic leukaemia	*Lymphomas*	*Tumour of central nervous system*	*Neuroblastoma*	*Genetic retinoblastoma*	*Non-genetic retinoblastoma*	*Wilms' tumour*	*Malignant bone*	*Soft tissue*	*Other neoplasms*	*All neoplasms*
Recurrent tumour	78 (95)*	97 (79)	260 (79)	15 (63)	8 (26)		8 (36)	23 (79)	24 (67)	37 (65)	550 (74)
Medical condition (related to treatment)	2 (2)	10 (8)	28 (8)	4 (16)			2 (9)	1 (3)	1 (3)	1 (2)	49 (7)
Second primary tumour		2 (2)	12 (4)	2 (8)	20 (65)	3 (60)	7 (32)	3 (10)	4 (11)	8 (14)	61 (8)
Accident, suicide, or homicide		6 (5)	17 (5)	1 (4)	1 (3)	1 (20)	2 (9)	1 (3)	1 (3)	4 (7)	34 (5)
Other cause (unrelated to tumour or its treatment)	2 (2)	8 (6)	12 (4)	2 (8)	2 (6)	1 (20)	3 (14)	1 (3)	6 (17)	7 (12)	44 (6)
Unsufficient information	2	1	5					1	2		11
Total deaths	84	124	334	24	31	5	22	30	38	57	749
Total No of 5 year survivors	171	538	1257	230	267	287	365	151	352	464	4082

*% Of deaths is based on the number of deaths with sufficient information to code the cause.

Table 2 Frequency of different causes of death observed at varying times from diagnosis

	No of 5 year survivors	*Causes of death 5–9 years from diagnosis*					*No of 10 year survivors*	*Causes of death 10–14 years from diagnosis*				
		Recurrent tumour	*Related medical condition**	*Second primary tumour*	*Accident†*	*Other cause‡*		*Recurrent tumour*	*Related medical condition**	*Second primary tumour*	*Accident†*	*Other cause‡*
Acute lymphoblastic leukaemia	171	70	2			2	95	6				
Hodgkin's disease	328	70	4	1	3		247	9	4			1
Non-Hodgkin lymphoma	203	12	1		2	2	181					1
Tumours of central nervous system	1257	163	12	2	5	1	1066	56	4	2	7	4
Neuroblastoma	230	11					219	2	1			2
Genetic retinoblastoma	267	6		3	1	1	256	1		8		
Non-genetic retinoblastoma	287						283			1		
Wilms' tumour	365	7	1				354			1		
Osteosarcoma	73	6	1	1			65					
Ewing's sarcoma	40	10					30	1				
Soft tissue sarcomas	352	18	1	1		1	326	5		2		1
Other neoplasms	509	35		3		2	467	4	1	2	1	1
All neoplasms	4082	408	22	11	11	9	3589	84	10	16	8	10

The number of patients who survive to a specified time does not equal the number surviving in the previous time interval plus deaths in the interim

*Medical condition related to treatment of the tumour.

†Traumatic death unrelated to tumour or its treatment—that is, accident, suicide, or homicide.

‡Any other cause unrelated to tumour or its treatment.

Table 3 Deaths not directly related to tumour or its treatment (n=44)

Original diagnosis	*Cause of death*	*Associated condition*	*Interval from diagnosis to death (years)*
Hodgkin's disease	Coronary atherosclerosis		21
Hodgkin's disease	Coronary atherosclerosis		20
Non-Hodgkin lymphoma	Coronary atherosclerosis	Diabetes mellitus	11
Osteosarcoma	Coronary atherosclerosis	Addison's disease, diabetes mellitus	18
Fibrosarcoma	Coronary atherosclerosis		30
Fibrosarcoma	Coronary atherosclerosis		23
Melanoma of eye	Coronary atherosclerosis		23
Thymoma	Coronary atherosclerosis	Aortic valve incompetence	13
Ependymoma	Congenital heart disease		5
Astrocytoma	Congestive cardiac failure	Severe kyphoscoliosis	13
Non-Hodgkin lymphoma	Cerebrovascular accident	Chronic renal failure	35
Astrocytoma	Cerebrovascular accident	Disseminated lupus erythematosus	12
Astrocytoma	Cerebrovascular accident		20
Cancer of thyroid	Cerebrovascular accident	Malignant hypertension	16
Epithelioma	Cerebrovascular accident		28
Neuroblastoma	Cerebrovascular accident		12
Dysgerminoma	Cerebrovascular accident	Malignant hypertension	16
Astrocytoma	Pulmonary embolus/deep venous thrombosis	Postpartum	15
Astrocytoma	Pulmonary embolus/deep venous thrombosis	Tegretol hepatitis	23
Medulloblastoma	Cor pulmonale/bronchiectasis	Hypogammaglobulinaemia	22
Retinoblastoma	Pneumonia	Mental retardation	7
Astrocytoma	Pneumonia		13
Acute lymphoblastic leukaemia	Chicken pox pneumonia		5
Tumour of central nervous system	Aspiration pneumonia	After oesophageal dilatation	28
Rhabdomyosarcoma	Apiration pneumonia	After fit	21
Optic nerve glioma	Meningitis		12
Wilms' tumour	Encephalitis		19
Dysgerminoma	Streptococcal septicaemia	Diabetes mellitus	7
Retinoblastoma	Acute renal failure		55
Fibrosarcoma	Acute renal failure		6
Non-Hodgkin lymphoma	Chronic renal failure		7
Wilms' tumour	Chronic renal failure		23
Neuroblastoma	Chronic renal failure	Spina bifida	11
Retinoblastoma	Diabetic ketoacidosis		15
Optic nerve glioma	Hypoglycaemic coma	Diabetes mellitus	16
Hodgkin's disease	Cirrhosis	Collagenosis	16
Non-Hodgkin lymphoma	Acute hepatitis		6
Astrocytoma	After cholecystectomy		38
Wilms' tumour	After mitral valve replacement		30
Langerhans cell histiocytosis	After aortic valve replacement		7
Hodgkin's disease	Gastric ulcer		13
Fibrosarcoma	Intestinal obstruction		14
Fibrosarcoma	Motor neurone disease		44
Acute lymphoblastic leukaemia	Cerebral degeneration		9

examination report for 150 (80%). A postmortem examination report was obtained for 40 (21%) of these deaths.

Of the deaths occurring from causes other than recurrent disease, 44 (6%) were due to causes not directly related to the tumour or its treatment (table 3). However, 49 (7%) of the deaths in five year survivors occurred from medical conditions related to treatment (table 4). The major causes of death in this group included infection (n=16), problems related to radiotherapy (n=13), and adrenal failure (n=7).

Traumatic deaths due to accidents, suicide, or homicide accounted for 5% of the deaths in five year survivors.

Table 5 gives the proportion of five year survivors subsequently dying of recurrent tumour within the next 15 years. Deaths from causes

No of 15 year survivors	*Causes of death 15–19 years from diagnosis*					*No of 20 year survivors*	*Causes of death 20+ years from diagnosis*				
	Recurrent tumour	*Related medical condition**	*Second primary tumour*	*Accident†*	*Other cause‡*		*Recurrent tumour*	*Related medical condition**	*Second primary tumour*	*Accident†*	*Other cause‡*
87	1					22	1				
231	3	1			1	133	2		1	1	2
180	1					121					1
986	26	4	4	3	2	658	15	8	4	2	5
214	2	2				151		1	2	1	
247	1		5			189			4		1
282				1	1	191			2		
352		1	3	1	1	220	1		3	1	2
65	1				1	46			2		
29	1					19					
314	1					240			1	1	4
456	1		1	2	2	316	1		2	2	2
3443	38	8	13	7	8	2306	20	9	21	8	17

because of losses to follow up.

other than recurrent tumour were regarded as losses to follow up. Less than 10% of five year survivors of non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilms' tumour, or a soft tissue sarcoma died of recurrent tumour during the next 15 years. In contrast, almost half of the five year survivors of acute lymphoblastic leukaemia died from recurrent disease during a similar period. Late relapse and death were also common in Hodgkin's disease, ependymoma, medulloblastoma, and Ewing's tumour with more than a quarter of the five year survivors dying of recurrent tumour within the subsequent 15 years.

Table 6, derived from death certificate coding, gives a comparison of the observed and expected number of deaths from particular neoplasms for which it is possible to define a range of ICD codes, which is almost certain to include any death from recurrent tumour. A measure of the excess number of deaths observed compared with that expected is also given in table 6 and may be interpreted as the extra number of deaths observed in the study population, from the neoplasms specified, per 100 patients per year. Inspection of table 6 indicates that the excess number of neoplastic deaths among five year survivors of retinoblastoma, non-Hodgkin lymphoma, and Wilms' tumour was consistently less than one extra death per 100 patients per year. The excess among survivors of Hodgkin's disease, tumours of the central nervous system and bone tumours did not exceed five extra deaths per 100 patients per year. The largest excess observed was after acute lym-

Table 4 Deaths from medical conditions related to treatment of the tumour (n=49)

Original diagnosis	*Cause of death*	*Related treatment factor*	*Interval from diagnosis to death (years)*
Ependymoma	Meningitis	After surgery for recurrence	10
Medulloblastoma	Meningitis	After surgery for recurrence	5
Astrocytoma	Ventriculitis	Ventriculoatrial shunt infection	20
Glioma	Ventriculitis	Ventriculoatrial shunt infection	16
Astrocytoma	Syringomyelia	Radiotherapy necrosis of spinal cord	18
Astrocytoma	Syringomyelia	Radiotherapy necrosis of spinal cord	18
Glioma fourth ventricle	Acute brain stem syndrome	Obliteration of cerebral vasculature after radiotherapy	25
Astrocytoma	Cerebral degeneration	Obliteration of cerebral vasculature after radiotherapy	26
Astrocytoma	Hydrocephalus	Gliosis at base of brain after radiotherapy	25
Astrocytoma	Hydrocephalus	Shunt dysfunction	10
Astrocytoma	Hydrocephalus	After cisternostomy	6
Ependymoma	Hydrocephalus	Tentorial herniation	5
Craniopharyngioma	Aspiration pneumonia	Ischaemic necrosis of frontal lobe after surgery	8
Glioma fourth ventricle	Aspiration pneumonia	After fit due to recurrrence	9
Medulloblastoma	Status epilepticus	Mental retardation	18
Craniopharyngioma	Cerebroatherosclerosis	After radiotherapy	26
Craniopharyingioma	Intracranial venous thrombosis	After surgery for recurrence	6
Craniopharyngioma	Addisonian crisis		9
Craniopharyngioma	Addisonian crisis	Pneumonia	9
Craniopharyngioma	Addisonian crisis	Gastroenteritis	7
Craniopharyngioma	Addisonian crisis		7
Craniopharyngioma	Addisonian crisis	Tonsillitis	9
Craniopharyngioma	Addisonian crisis	Respiratory tract infection	12
Craniopharyngioma	Addisonian crisis		22
Craniopharyngioma	Bronchopneumonia		28
Medulloblastoma	Bronchopneumonia	After surgery	24
Acute lymphoblastic leukaemia	Pneumococcal meningitis	On chemotherapy	6
Hodgkin's disease	Cryptococcal meningitis	On chemotherapy	6
Hodgkin's disease	Cryptococcal meningitis	On chemotherapy	13
Hodgkin's disease	Pelvic abscess	On chemotherapy	8
Hodgkin's disease	Pneumococcal meningitis	After splenectomy	18
Hodgkin's disease	Subphrenic abscess	After splenectomy	12
Hodgkin's disease	Disseminated zoster	On chemotherapy	6
Hodgkin's disease	Disseminated zoster	On chemotherapy	12
Hodgkin's disease	Cor pulmonale	Pulmonary fibrosis after radiotherapy	7
Neuroblastoma	Cor pulmonale	Pulmonary fibrosis after radiotherapy	16
Wilms' tumour	Cor pulmonale	Pulmonary fibrosis after radiotherapy	17
Wilms' tumour	Peritonitis	Perforated bowel ?due to radiotherapy	6
Neuroblastoma	Peritonitis	Chronic renal failure	20
Neuroblastoma	Cholangitis	Periportal fibrosis after radiotherapy	13
Non-Hodgkin lymphoma	Acute liver failure	After radiotherapy for recurrence	5
Hodgkin's disease	Hypertensive encephalopathy/ chronic renal failure	Radiation nephritis	12
Glioma spinal cord	Chronic renal failure	Neurogenic bladder	5
Neurofibrosarcoma	Chronic renal failure	Neurogenic bladder	7
Histiocytosis X	Hyperosmolar coma	Diabetes insipidus	14
Ganglioneuroblastoma	Haemorrhage	Intraoperative	15
Osteosarcoma	Haemorrhage	After pneumonectomy	8
Astrocytoma	Anaesthetic death	Unsuspected phaechromocytomas	19
Acute lymphoblastic leukaemia	Severe anaemia	Parents Jehovah's witnesses	6

Table 5 Actuarial percentage of five year survivors subsequently dying of recurrent tumour

Diagnosis	*No of 5 year survivors*	*% (SE) of 5 year survivors dying of recurrent tumour by 20 years from diagnosis*
Acute lymphoblastic leukaemia	171	47 (4)
Lymphomas:	538	18 (2)
Hodgkin's disease	328	26 (3)
Non-Hodgkin lymphoma	203	6 (2)
Tumours of central nervous system:	1257	20 (1)
Ependymoma	123	26 (4)
Astrocytoma	670	15 (1)
Medulloblastoma	165	34 (4)
Neuroblastoma	230	6 (2)
Retinoblastoma:		
Genetic	267	3 (1)
Non-genetic	287	0
Wilms' tumour	365	2 (1)
Malignant bone tumours:	151	15 (3)
Osteosarcoma	73	10 (4)
Ewing's tumour	40	30 (7)
Soft tissue sarcoma:	352	7 (1)
Rhabdomyosarcoma	87	7 (3)
Fibrosarcoma	175	5 (2)

phoblastic leukaemia and exceeded 10 extra deaths per 100 patients per year.

Table 7, again using information from death certificates only, gives the results of comparing the observed and expected number of deaths from all causes other than neoplasm. Threefold the expected number of non-neoplastic deaths were observed. We observed 13-fold the number of deaths expected from infections other than pneumonia and influenza. The excess of deaths assigned to pneumonia and influenza, particulary after central nervous system tumours, needs careful interpretation because of the tendency of many clinicians to record bronchopneumonia as the cause of death in patients with recurrent tumours of the central nervous system, but may also reflect the problem of prolonged impairment of immunity in patients with a history of cancer. Of the eight

Table 6 Comparison of observed and expected deaths from neoplastic causes

	Interval from diagnosis in years					
	5–9			*10+*		
	Observed (O)	*Expected (E)*	*Excess**	*Observed (O)*	*Expected (E)*	*Excess**
Acute lymphoblastic leukaemia	71	0·009	12·5	7	0·007	0·9
Hodgkin's disease	70	0·011	5·1	17	0·035	0·6
Non-Hodgkin lymphoma	8	0·006	0·9	1	0·022	0·0
Tumour of central nervous system	141	0·085	2·5	89	0·210	0·7
Genetic retinoblastoma	5	0·000	0·4	2	0·000	0·1
Non-genetic retinoblastoma	0	0·000	0·0	0	0·000	0·0
Wilms' tumour	8	0·004	0·4	2	0·005	0·0
Malignant bone tumour	14	0·005	2·1	2	0·007	0·1

$$\text{*Excess}=\left\{\frac{(\text{O}-\text{E})\ 100}{\text{person years}}\right\}$$

Table 7 Comparison of observed and expected deaths from non-neoplastic causes five or more years from diagnosis

	Infectious/parasitic diseases	Endocrine, nutritional, and metabolic diseases	Diseases of the nervous system and sense organs	Diseases of the circulatory system	Pneumonia and/or influenza	Diseases of the digestive system	Diseases of the genitourinary system	Congenital diseases	Medical misadventure	Other accidents	Suicide	Uncertain whether accident, suicide, or homicide	Other non-neoplastic causes	All non-neoplastic causes of death
Acute lymphoblastic leukaemia:														
Observed	2	0	0	0	0	0	0	0	0	0	0	0	0	2
*O/E	178													4
p Value	0·000													0·102
Lymphomas:														
Observed	4	1	0	6	1	1	0	0	0	5	1	0	0	19
*O/E	50	10		9	6	7				2	2			4
p Value	0·000	0·096		0·000	0·148	0·137				0·067	0·428			0·000
Tumours of central nervous system:														
Observed	0	4	2	4	10	2	1	1	1	11	1	2	3	42
*O/E		17	3	3	28	7	6	3	81	3	1	5	3	4
p Value		0·000	0·119	0·040	0·000	0·038	0·159	0·304	0·012	0·004	0·635	0·057	0·054	0·000
Embryonal tumours:														
Observed	1	1	0	1	2	0	1	2	2	4	1	0	0	15
*O/E	5	4		1	6		8	4	225	1	1			2
p Value	0·178	0·222		0·502	0·045		0·123	0·080	0·000	0·558	0·485			0·028
Malignant bone tumours:														
Observed	0	0	0	2	0	0	0	0	0	0	1	0	0	3
*O/E				9							7			2
p Value				0·023							0·139			0·155
Soft tissue sarcoma:														
Observed	0	0	1	2	1	1	0	2	0	0	0	0	2	9
*O/E			5	5	9	10		16					7	3
p Value			0·176	0·065	0·108	0·093		0·007					0·030	0·006
Other neoplasms:														
Observed	1	2	0	5	0	0	0	1	0	2	1	1	0	13
*O/E	13	21		11				7		1	3	6		3
p Value	0·073	0·004		0·000				0·140		0·474	0·318	0·142		0·000
All neoplasms:														
Observed	8	8	3	20	14	4	2	6	3	22	5	3	5	103
*O/E	13	10	1	5	12	4	4	5	79	2	2	2	2	3
p Value	0·000	0·000	0·314	0·000	0·000	0·016	0·101	0·002	0·000	0·031	0·207	0·129	0·141	0·000

*Observed/expected.

deaths coded to endocrine or metabolic causes, two deaths were due to the metabolic complications of diabetes mellitus, one death was from hyperosmolar coma secondary to diabetes insipidus in a patient with Langerhans cell histiocytosis, and one death was due to cor pulmonale secondary to severe bronchiectasis resulting from recurrent infections in a patient with hypogammaglobulinaemia. In the remaining four cases, the cause of death on the death certificate was inaccurate as inspection of the notes indicated that death was due to recurrent tumour. However, excluding the latter four deaths still leaves an excess (one tailed $p=0·01$).

The fivefold excess of cardiovascular deaths were predominantly myocardial infarction or cerebrovascular accidents, which occurred at a younger age than expected for these conditions. There were eight deaths due to myocardial infarction; two patients had diabetes mellitus which may have contributed to the early onset of coronary atheroma. It is of interest that three patients had received radiotherapy to the mediastinum and one to the left infraclavicular region. Seven patients, aged 26–42 years, died from cerebrovascular accidents, three patients had previously received direct irradiation to some part of the brain. Three of the cerebrovascular accidents occurred in patients who had documented severe hypertension, one resulted from a subarachnoid haemorrhage secondary to a berry aneurysm, two were unexplained and the remaining patient, treated for a craniopharyngioma, was found to have extensive cerebroatherosclerosis at necropsy. Of the remaining cardiovascular deaths, one was due to left ventricular failure in a patient with severe hypertension and chronic renal failure, and one to congestive cardiac failure in a patient with severe kyphoscoliosis. In three cases the certified cause of death from circulatory causes was inaccurate as examination of the patient's records indicated that they had actually died from the effects of recurrent disease and the death certificates in these cases were, therefore, misleading. However, even after excluding these three deaths there was still an excess of cardiovascular deaths (one tailed $p<0·001$).

There was fivefold excess of deaths from congenital causes as coded from the death certificate. Of the six deaths thus coded, three were in patients with von Recklinghausen's disease, one of the patients dying from renal failure which was tumour related and two from recurrent tumour. There were two further deaths from renal failure, one in a patient with Wilms' tumour and polycystic kidneys and one in a patient with neuroblastoma and spina bifida who had a neurogenic bladder and hydronephrosis. The final death in this category was due to mechanical failure of an aortic valve prosthesis in a patient with congenital heart disease.

Considering all neoplasms as a single group there was no evidence of an excess of deaths from suicides. The excess of deaths from accidents other than medical misadventure was predominantly due to observing threefold the expected number of accidents after tumours of the central nervous system. A total of 11 patients who had been treated for these tumours died from accidents. Six of these patients (aged 10 to 35) died in road traffic accidents, two teenagers died from burns caused by accidental fires and hot water scalds at home, and two patients from complications after falls. The final death was due to manual strangulation, but in what circumstances this occurred is uncertain. Apart from one child with an optic nerve glioma who was visually handicapped we can only speculate that the effect of the tumour or treatment had resulted in some sensory or intellectual impairment that increased the risk of these patients becoming involved in accidents.

Discussion

Ascertaining the cause of death in a population of children who were diagnosed before 1971 was not easy as some hospitals destroy medical records at a specified number of years after death, and even when records were available, it was sometimes difficult to be completely sure of the actual cause of death. Fortunately, in the present study, we obtained hospital notes or a postmortem examination report for 80% of the deaths from causes other than recurrent tumour. We were most confident of our assessment where a postmortem examination report was available.

The good long term prospects for five year survivors of childhood non-Hodgkin lymphomas, neuroblastoma, retinoblastoma, Wilm's tumour, and soft tissue sarcoma, treated before 1971, are confirmed in our study with less than 10% dying of recurrent tumour during the subsequent 15 years.

For all types of childhood neoplasm the results of our study are similar to those of Li *et al* who reported on 2232 five year survivors of a variety of childhood cancers diagnosed before 1970.[7] Our findings are also similar to those of Taylor and Potish who reported on 37 deaths occurring among 189 five year survivors of childhood cancer treated with megavoltage radiotherapy between 1953 and 1975.[8]

Our study indicates that in children with central nervous system tumours, deaths from recurrent tumour were still occurring more than 20 years from diagnosis. Many central nervous system tumours, particularly low grade astrocytomas and craniopharyngiomas, are relatively slow growing and so deaths may occur many years after the initial diagnosis. It is also recognised that both Hodgkin's disease and Ewing's tumour are indolent tumours and multiple relapses responding to further treatment can occur over a period of several years before eventual death from disease occurs.

The high frequency of deaths from recurrent disease after acute lymphoblastic leukaemia is partly explained by a large number of central nervous system relapses occurring during an era when children were not routinely given central nervous system irradiation and intrathecal methotrexate to reduce the risk of meningeal leukaemia. Central nervous system leukaemia may take a very indolent course, being partially controlled for long periods, and it may be several years before either a subsequent bone marrow relapse occurs or the child develops resistant central nervous system disease. In addition, some children with meningeal leukaemia may develop an encephalopathy from the combination of repeated cranial irradiation and intrathecal methotrexate and this may not become manifest until several years after treatment.

In our study second primary tumours as a cause of death were relatively more commonly seen in patients with genetic retinoblastoma and Wilms' tumour. We have reported on the pattern and incidence of second primary tumours among survivors of childhood cancer elsewhere.[9 10]

Of the 49 deaths from causes related to treatment, at least 21 occurred in children undergoing treatment for recurrent disease and these deaths were probably unavoidable due to the intensity of treatment required in the presence of resistant disease. However, it is possible that a number of the remaining 28 deaths might have been preventable. The main cause of potentially avoidable death was from endocrine failure (n=7) in children with craniopharyngioma and panhypopituitarism who presented with addisonian crises in periods of stress related to infection. It is possible that the need for high doses of intravenous corticosteroids, which might have been life saving, was not recognised in these cases.

The other major cause of death related to primary treatment was from problems secondary to post radiation fibrosis. Five children with astrocytoma developed radiation related central nervous system degeneration, three children developed pulmonary fibrosis after whole lung irradiation and three children developed fibrosis of abdominal organs after abdominal irradiation. It is very difficult to know whether these problems could have been avoided by a more judicious approach to radiotherapy. However, in some cases radiation was given for recurrent disease and therefore the effect of radiation was probably unavoidable.

The only previous study of potentially avoidable deaths after diagnosis of childhood cancer was a Finnish study of mortality among 100 children diagnosed with acute lymphoblastic leukaemia, between 1975 and 1981.[11] This study identified five deaths from infections occurring during induction or primary remission that might have been avoided.

Of the 44 late deaths in our study classified as being unrelated to the primary cancer or its treatment the most frequently occurring cause of death was due to cardiovascular disease (n=20), including eight deaths due to coronary atherosclerosis and seven due to cerebrovascular accidents. Four of the eight deaths occurred in patients who had received mediastinal or chest irradiation and it is possible that the irradiation may have contributed to the early development of coronary atheroma. All the patients dying from coronary artery disease were relatively young at the time of death (age range 23–45 years). There were eight deaths from infection in patients who were off treatment and in remission from their cancer. This highlights the point that children may remain relatively immunocompromised for many years after treatment.

A previous report of an excess of cerebrovascular accidents in children diagnosed with cancer identified 26 such cases among 700 children.[12] The average follow up interval was short, however, and all of the deaths occurred a median time of five months after diagnosis. Results from this study taken together with those from our study indicate that survivors of childhood cancer are at an increased risk of cardiovascular death immediately after diagnosis and remain so beyond five years from diagnosis, although the aetiology of these early and late deaths are almost certainly different.

In conclusion we observed a five times expected excess of deaths due to cardiovascular causes, with deaths from myocardial infarction and cerebrovascular accidents being most frequent. The long term effects of radiation on the coronary vasculature of children have not been established but there is obvious concern that radiotherapy may predispose to the early development of coronary atheroma. The excess number of cerebrovascular accidents did not appear to be due to a direct effect of radiotherapy on the cerebral vasculature.

Among the deaths classified as being related to treatment we identified two groups of potentially avoidable deaths. One group consisted of children with craniopharyngioma and secondary hypothalamic-pituitary dysfunction, after surgery and radiotherapy, who died from adrenal failure during periods of stress. The other group consisted of children who received inappropriate doses of radiation and died from problems related to radiotherapy fibrosis.

We emphasise that our investigation relates to patients treated for childhood cancer before 1971 and who were treated predominantly by surgery and radiotherapy. The pattern of mortality after more recent treatment regimens, in which chemotherapy has been used extensively and radiotherapeutic techniques have been refined, are likely to be different. With the knowledge of the potential long term effects of treatment, it is hoped that future protocols can be planned to reduce the risk of late treatment related deaths. The information gained from the study of late deaths should also be of value in helping give appropriate advice and monitor the health of potentially 'at risk' groups of patients.

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Forty years ago

The 1950 volume of the *Archives of Disease in Childhood* contained papers by two paediatric pathologists. At the time of publication Ian Cathie was haematologist to the Hospital for Sick Children, Great Ormond Street, and Albert Claireaux was to become its morbid anatomist some years later.

Congenital hypoplastic anaemia

Congenital hypoplastic anaemia is characterised by the onset in the first few weeks of life of a severe normocytic, normochromic anaemia. The peripheral blood shows normal white cells and platelets but no reticulocyte response to the anaemia. The marrow contains normal myeloid precursors and megakaryocytes but grossly reduced normoblasts.

Cathie described five patients with these findings and noted a characteristic facies common to all five—tow coloured hair, snub nose, thick upper lip, wide set eyes, and an intelligent expression.[1] The only treatment available was repeated blood transfusion and Cathie commented on the need to resort to tranfusing packed cells into the external jugular veins when all the peripheral limb veins had been tied off after several years of transfusions by the 'cut down' technique. (Elderly readers of this journal who were house physicians at Great Ormond Street in the late 1940s will remember these five patients only too well.)

An interesting feature of this paper was Cathie's discussion of the nomenclature of the disease. He considered 'congenital hypoplastic anaemia', the term which had been used by Blackfan and Diamond in the United States, to be inaccurate and suggested 'erythrogenesis imperfecta' which better described what he felt was a failure of red cell maturation. This term was used in the UK for some time but others, such as 'Blackfan-Diamond syndrome' and 'pure red cell aplasia' became more popular.

Haemolytic disease of the newborn

Claireaux reported a study of 157 cases of haemolytic disease of the newborn collected between 1938 and 1947 in Edinburgh.[2]

There were 36 cases of hydrops fetalis, of whom 31 were stillborn and five died within hours of birth. In a further 110 babies there was an early onset of severe jaundice (icterus gravis neonatorum). The overall mortality in the jaundiced group was 70%, with the highest mortality in those whose jaundice developed at birth or within 24 hours. Eleven babies had haemolytic anaemia without severe jaundice and of these three died.

Late in 1947 the direct Coombs test became available and was carried out on all babies from then on. Serum bilirubin concentrations were measured in most cases of severe jaundice and ranged from 2 to 20 mg/100 ml (34 to 340 μmol/l). Babies with concentrations over 7 mg/100 ml (119 μmol/l) at birth seldom recovered.

Treatment was simple transfusion of Rh negative blood in quantities of 15 ml/pound body weight, repeated as necessary. At first the anterior fontanelle was used, then the saphenous vein at the ankle, and only in the later cases was transfusion given by the umbilical vein. Of 35 babies treated by simple transfusion 17 died. The author reported that a new transfusion technique (exchange transfusion) was being tried at the time of writing but that the early results were less satisfactory than had been anticipated.

Kernicterus did not develop in any baby before the age of 18 hours but was present in 37 (34%) of the cases of severe jaundice. The serum bilirubin concentrations in babies with kernicterus ranged from 10 to 20 mg/100 ml (170 to 340 μmol/l). All but two of the babies with kernicterus died: 33 within two weeks of birth. Four babies survived beyond the age of 2 weeks: two died in infancy and two survived to develop cerebral palsy.

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ADM JACKSON

Diagnosis of Pneumocystis carinii pneumonia from non-invasive sampling of respiratory secretions

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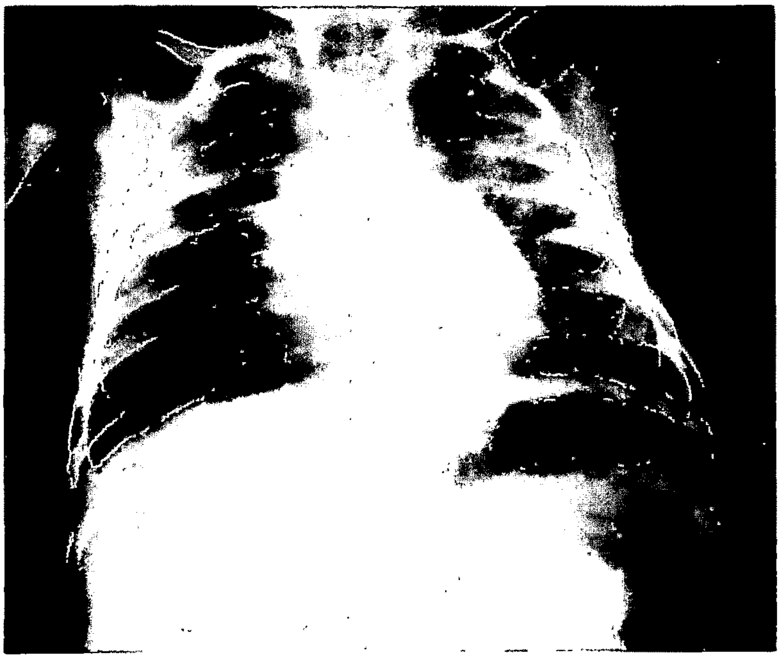
Abstract

An infant infected with HIV presented with fever, tachypnoea, hypoxia, and radiological evidence of bilateral pneumonitis. Fluorescent antibody technique identified *Pneumocystis carinii* within 24 hours from secretions obtained by nasopharyngeal aspiration. This rapid, non-invasive method should be the first line investigation of suspected *P carinii* pneumonia in immunocompromised patients.

Pneumocystis carinii is an important pathogen in the immunocompromised child, and must be considered in the differential diagnosis of any such child presenting with respiratory symptoms. Characteristic radiological appearances are of diffuse reticulogranular infiltrates, particularly in the perihilar region, progressing to consolidation, but a normal chest radiograph is compatible with the diagnosis.[1] Cytomegalovirus or mycobacteria infection may produce similar findings.

Definitive diagnosis has previously relied on the demonstration of silver staining cysts in material obtained from open lung biopsy or bronchioalveolar lavage, requiring an invasive procedure in an acutely ill child.[2 3] Sputum induction in infants and small children is not a practicable technique,[4] and serology is unhelpful.[5] We report a case in whom the diagnosis was made from nasopharyngeal secretions using a fluorescent antibody technique.



Chest radiograph showing bilateral interstitial pneumonitis.

Case report

A white infant girl whose HIV seropositive mother developed *P carinii* pneumonia at 35 weeks' gestation was delivered at term weighing 3050 g. There were no neonatal problems, and her initial progress was complicated only by persistent candidal infection of the oral cavity and napkin area.

At 4·5 months she presented with a two week history of mild upper respiratory symptoms, two days of fever, an unproductive cough, and increasing tachypnoea, sufficiently severe to impair feeding. Examination showed a pale, mildly cyanosed and lethargic, but responsive infant. She had a tachycardia of 160/minute and respiratory rate of 80/minute, with bilateral intercostal and subcostal indrawing and scattered crepitations on auscultation. Lymphadenopathy and hepatosplenomegaly were noted and there was candidal dermatitis of the napkin area.

A chest radiograph showed extensive bilateral pneumonitis (figure). She was hypoxic (oxygen saturation 60%), with a carbon dioxide tension (PCO_2) of 5·37 kPa and hydrogen ion concentration of 39·7 mmol/l. On admission the neutrophil count was 6200×10^6/l, T4 lymphocyte count 1079×10^6/l, and T4/T8 ratio 1·4. Serum IgG concentration was normal (4 g/l), and IgA and IgM raised (0·9 g/l and 2·1 g/l). HIV p24 antigen was positive (140 pg/ml). Secretions obtained by nasopharyngeal aspiration were sent for microbiological investigation.

Pending results the infant received oxygen supplementation and high dose cotrimoxazole and acyclovir intravenously. The identification of *P carinii* was confirmed the next day (see below). The infant's condition initially stabilised, but deteriorated 24 hours later. Despite giving hydrocortisone and intravenous immunoglobulin, she failed to maintain oxygen saturation of >80% even with fractional inspiratory oxygen of 100%, and developed carbon dioxide retention (PCO_2 9·75 kPa) and respiratory acidosis (hydrogen ion concentration 73·7 mmol/l). Definite knowledge of the diagnosis, and its implications for the child's long term prognosis meant that the parents could be counselled appropriately. Their wish for her not to receive mechanical ventilation was respected, and she died on the fourth day of her admission. Postmortem examination confirmed the widespread alveolar exudate within the lungs in which round organisms were detected by silver staining. No other organisms were detected.

Method

After addition of an equal volume of sputolysin (Behring Diagnositics) and glass beads the sample was vortexed for one minute and the incubated at 37°C for three minutes. A total of 10 ml of phosphate buffered saline (PBS) pH 7·2 was added and the mixture centrifuged at 2500 *g* for 20 minutes. The pellet was resuspended in 1 ml PBS and cytospin preparations made on two polyl-lysine coated slides. A cytospin preparation of positive rat lavage material was used as a positive control. After fixation for 30 minutes in equal volumes (50%) methanol and acetone, trypsin (0·25%) digestion for 10 minutes at 37°C followed. A standard wash procedure of three five minutes with PBS was carried out.

Mouse monoclonal antibody to *P carinii* (Northumbria Biologicals Limited) was added to the test and positive control slides and PBS only, and incubated for 40 minutes. After repeat washing antimouse IgG (F'ab) conjugated to fluorescein isothiocyanate was added and a further incubation of 40 minutes followed. After a last wash procedure substituting PBS pH 8·4 for the final change, the slides were mounted and viewed under ultraviolet light.

The sample was considered positive when three typical cysts showing all over fluorescence were seen, further confirmed by methenane silver treatment of the control slide.

Discussion

In HIV infection, the diagnosis of *P carinii* pneumonia has important implications, not only for the treatment of the acute illness, but also for longer term prognosis. In New York 13 out of 15 children less than 6 months old with *P carinii* pneumonia died during the acute episode, and all were dead by one year (J Chow, K Shah, K Li, *et al*; abstract presented at V International Conference on AIDS, Montreal, June 1989. Because of the risks involved in, and the technical expertise required for, paediatric bronchoscopy treatment is usually empirical. If the child dies, postmortem examination may give the answers, but if the child responds to high dose cotrimoxazole, the differential diagnosis between a bacterial pneumonia and *P carinii* pneumonia remains unresolved. This then creates difficulties in classification and staging of the child's disease, and in making therapeutic decisions, such as whether to commence zidovudine or prophylaxis for *P carinii* pneumonia.

Identification of *P carinii* pneumonia from upper respiratory tract secretions may only be possible in cases of overwhelming infection, and failure to detect it by this method does not exclude the diagnosis. It is in the most severe cases, however, that the patient is least able to tolerate more invasive procedures. Because our technique is rapid, other methods can still be used thereafter without undue delay. We believe therefore that it should be used as the first line investigation of suspected *P carinii* pneumonia.

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Cystic fibrosis, Pseudomonas aeruginosa, and selective decontamination

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Abstract

We used an oral topical antibiotic preparation to try and prevent oropharyngeal carriage of *Pseudomonas aeruginosa* in patients with cystic fibrosis. Ten of 15 patients treated with a two week course of intravenous ceftazidime together with a 90 day course of an antibiotic containing gel continued to carry *P aeruginosa* in the oropharynx.

The technique of selective decontamination of the digestive system uses oral antibiotic combinations to prevent the overgrowth of certain groups of organism (typically Gram negative aerobes), and allows the more usual flora to maintain colonisation resistance.[1] It has application particularly in the immunocompromised patient undergoing cytotoxic chemotherapy and in long term ventilated patients,[2] where Gram negative aerobes normally confined to the large bowel may colonise first the oropharynx and then the lower respiratory tract.

The principle of selective decontamination has been previously adopted in cystic fibrosis patients carrying *Pseudomonas aeruginosa* when using antipseudomonal agents delivered by aerosol.[3] Although this treatment has been successful in reducing the number of pseudomonas isolates, and in reducing the frequency of lower respiratory tract exacerbations, it has proved impossible to eradicate *P aeruginosa*. This pilot study was conducted in order to find out whether an oral topical antibiotic preparation could prevent oropharyngeal carriage.

Subjects and methods

The study group comprised cystic fibrosis patients from whom *P aeruginosa* was isolated for the first time in consecutive oropharyngeal samples during a period of two weeks. All patients took flucloxacillin as prophylaxis against staphylococcal colonisation of the respiratory tract.

Patients were admitted to hospital regardless of clinical condition, and treated initially with intravenous ceftazidime (150 mg/kg/day) for 14 days. In addition a selective decontamination gel composed of a 2% mixture of polymyxin E, tobramycin, and amphotericin B in a 3·5% carboxymethyl cellulose base was applied topically to the buccal mucosa and gingiva four times a day after meals. On completion of the initial inpatient stay a further 76 days of oral gel application was completed at home.

Respiratory tract infections (both upper and lower) during the period of the study were treated on merit. Upper respiratory coryzal illness was treated with an additional oral antibiotic either amoxycillin, erythromycin, or trimethoprim, and lower respiratory infections unresponsive to the above antibiotics were treated with oral ciprofloxacin, nebulised aminoglycoside, or intravenous ceftazidime.

BACTERIOLOGICAL MONITORING

Weekly throat and rectal swabs, together with lower airway samples, were cultured prospectively throughout and subsequent to the treatment period. All samples were cultured both qualitatively and quantitatively.

Quantitative culture

An aliquot of 1 ml or 1 g of specimen was suspended in a sterile culture tube containing 9 ml of brain heart infusion (BHI broth, No 49, Lab M). All specimens were serially diluted (1:10 steps), subcultured onto solid media using the four quadrant method, and the tip of the swab was broken off into broth. The concentrations of micro-organisms were estimated on a scale of 1+ to 5+. If only broth was positive, the growth density was recorded as 1+ (according to $\leq 10^1$ colony forming units (cfu)/ml or g); macroscopic growth in the first quadrant scored 2+ (according to $\leq 10^3$ cfu/ml or g) etc.

Qualitative culture

Morphologically distinct colonies were isolated in pure culture and identified by standard procedures (analytical profile index 20 E, coagulase, etc). Antibiotic sensitivities were determined using a controlled disc diffusion method for each of the different isolates. The antibacterial agents used for flora suppression (polymyxin E, tobramycin) and for systemic treatment (ceftazidime) were tested.

Definitions

Oropharyngeal carriage was defined as the presence of identical pseudomonas species in any concentration in at least two consecutive throat swabs over a period of two weeks.

Infection of the upper respiratory tract was a clinical diagnosis based on rhinorrhoea and cough thought to be viral in origin in most cases. Infection of the lower airways was a microbiologically proved clinical diagnosis with the sample yielding 100 000 cfu/ml or more.

The effectiveness of the topical antimicrobial gel during this study was judged by the eradication and/or prevention of *P aeruginosa* carriage in the oropharynx. In addition, Fisher's exact test and Student's *t* test were used to compare respiratory exacerbations, the use of additional antibiotics, and weight gain during the study period and for the subsequent 90 days.

Results

Fifteen children (nine boys and six girls) with cystic fibrosis, mean age 7·5 years (18 months–15·6 years) were assessed. Three patients failed

Table 1 Clinical details of cystic fibrosis patients

Patient No	*Age at diagnosis (months)*	*Shwachman score when colonised*	*Age at which P aeruginosa colonised (months)*	*Continued P aeruginosa isolation during selective decontamination period*	*P aeruginosa isolation three months after selective decontamination period*
1	2	65	89	Yes	Yes
2	17	75	69	Yes	Yes
3	2	60	178	Yes	Yes
4	30	60	153	Yes	Yes
5	6	75	10	Yes	Yes
6	2	90	111	Yes	Yes
7	2	90	52	Yes	Yes
8	27	95	137	Yes	Yes
9	3	85	24	No	No
10	18	60	23	Yes	Yes
11	24	55	92	Yes	Yes
12	48	85	64	No	No

Table 2 Group data during and after the period of selective decontamination. Values are expressed as mean (range) for the group of 12 patients

	Selective decontamination period (90 days)	*90 Days after decontamination period*
No of episodes upper respiratory tract infections	0·8 (0–3)	1·1 (0–3)
No of episodes lower respiratory tract infections	1·9 (1–4)	1·8 (1–3)
Weight gain (kg)	1·9 (−0·6–5·75)	1·4 (0·15–3·3)
No of courses additional antibiotics	2·7 (1–5)	3 (2–6)

There was no significant difference for any of the above variables between the selective decontamination period and the subsequent 90 days.

to complete the study: one did not fulfill the entry criteria and two patients did not like applying the oral gel. Clinical details of the 12 patients who completed the study are shown in table 1.

Ten patients (83%) continued to yield *P aeruginosa* from the throat and sputum during the treatment period and from the oropharynx during the three months after completion of the study (p=0·3). *P aeruginosa* was intermittently cultured from rectal swabs taken from three patients during the study period.

Table 2 shows clinical data for the selective decontamination period and the subsequent 90 days. There was no detectable benefit to the patient during the selective decontamination period in terms of weight gain or reduced frequency of respiratory exacerbations.

Discussion

Together with *Staphylococcus aureus* and *Haemophilus influenzae, P aeruginosa* is the commonest isolate from the oropharynx of patients with cystic fibrosis. Sporadic isolates of *P aeruginosa* are not unusual in patients with cystic fibrosis, but once oropharyngeal carriage has occurred, eradication is rare. The application of an oral selective decontamination gel was of no benefit to 10 out of 12 patients in preventing carriage of *P aeruginosa* within the oropharynx. The organism ultimately colonises most patients and has at least two strategies to facilitate survival. Once established in the respiratory tract, mucoid variants are commonly found. The 'slime' probably protects colonies from host defences, and intramural proteins have been identified in *P aeruginosa*, which may protect against antibiotic attack. Pseudomonas is not an oropharyngeal commensal, nor is it cultured from stool unless a large inoculum (10^6) is ingested orally. Even then, in normal individuals colonisation of the bowel does not occur.[4] Three patients were identified as having pseudomonal colonisation of the bowel because of repeated isolates from rectal swabs during attempted oral selective decontamination.

The failure of a selective decontamination approach in cystic fibrosis may be due to a number of factors. Lindemann *et al* found that the orophyarynx is a reservoir for the organism which may colonise by virtue of its preferred attachment to altered epithelial surfaces in the oropharynx of cystic fibrosis patients.[5] In contrast to the success achieved in ventilated patients where an antibiotic containing paste has been effective,[2] it was necessary to use an antibiotic containing gel because of the unpalatability of paste. The mucosal contact time of the gel compared with paste may have reduced antibiotic effectiveness. The reasons why patients with cystic fibrosis are colonised by *P aeruginosa* are still unclear, and the difficulties encountered in trying to prevent carriage of the organism remain.

AMD is in receipt of a cystic fibrosis research fellowship.

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Nocturnal faecal soiling and anal masturbation

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Abstract

Two cases of late onset faecal soiling as a result of anal masturbation in children who were neither mentally handicapped nor psychotic were studied. The role of soiling in aiding the young person and his family to avoid separating and maturing is highlighted. We suggest that the association of anal masturbation and resistant nocturnal soiling may be unrecognised.

Faecal soiling is defined as disordered bowel function and control occurring in children over a certain age in the absence of any physical abnormality or disease.[1] The prognosis is good, with remission occurring before adulthood. This has made it difficult to assess the effectiveness of intervention.[2] A steady decline in symptoms was recorded from the age of 6 years in boys and 8 years in girls in the follow up of 186 children attending child psychiatric clinics.[3] All were clean by the age of 16 years, apart from two relapses, one at 17 and one at 19 years. It has been suggested that encopresis in adulthood is a feature of either psychotic disorder or severe mental handicap, and there have been reports of two instances of persistence into adulthood in which neurosis was the most prominent feature.[4]

We report two further cases of late onset faecal soiling persisting into adolescence without psychosis or mental handicap, but in which neurotic features were implicated. Anal masturbation was a feature of both cases, a factor not previously reported to our knowledge.

Case reports

CASE 1

At the age of 13 years a boy began to soil at night but not during the day. This always occurred at home. At the age of 17 he was referred for inpatient treatment after individual outpatient treatment had proved to be unsuccessful. While he was in a medical ward no physical abnormality was found and no soiling occurred.

The effect of his soiling within the home was that his mother prompted and controlled him in all areas of his life. Despite paid employment she took responsibility for his finances, she checked his clothes and bed each day, and absolved him from any household tasks.

He had no contact with his father who had left when he was 4 years old. His mother had a fiancé of 11 years' standing, but no plans to marry 'until the children leave home'.

His early developmental history was unremarkable. He had attended the local comprehensive school where he was of below average ability. On leaving school he obtained employment as a manual worker.

On direct questioning he readily admitted to inserting fingers into his anus since the age of 13. He stated that this had started as a means of overcoming feelings of constipation but admitted that it was now a habit that he enjoyed. He claimed to be heterosexually active without any homosexual feelings or desires. He had no recollection of being sexually abused. His mother acknowledged that she had been aware of his action but had not volunteered the information previously.

He was admitted for inpatient treatment consisting of a behavioural toileting programme and an emphasis on developing selfhelp and independent living skills. There were also meetings with his mother aimed at changing their unhelpfully close relationship. Under this plan he rapidly became clean and was able to maintain this for weekend visits at home. His mother, however, became increasingly anxious and upset at the distance she felt was being created between them. She found it difficult to look at her own circumstances and to face the reality of personal decisions she had been postponing.

At the time of discharge, therefore, the acute problems had resolved but the underlying family problems were unchanged.

CASE 2

A boy who had been soiling at night since he was 9 years old was referred to local and regional child psychiatric units when he was 13·5 years old. After referral his soiling ceased rapidly, only to relapse subsequently.

Admission to a child psychiatric inpatient unit was refused by the family. No physical abnormality or cause was found, and his stools were normally formed. He was reported to be a friendly boy with good peer and school relationships.

He came from an over close family in which the solution to his soiling was for him to sleep in the same room as another member of the family. On these nights he would not soil.

When referred to an adolescent unit at the age of 17 he was directly questioned about anal masturbation. He admitted inserting fingers into his anus and manually evacuating faeces into his underwear.

During psychotherapy he acknowledged that he derived pleasure from the insertion and evacuation. He emphasised his heterosexuality and denied any recollection of having been sexually abused. In the course of these individual sessions there was symptomatic improvement. When contacted by the unit 12 months later his soiling and masturbation were still continuing, but he did not keep further appointments.

Discussion

Published reports about anal masturbation in association with faecal soiling are few. Though there is some anecdotal evidence its prevalence is unknown.[1] The rarity of pure nocturnal soiling is also highlighted with particular reference to the difficulty of treatment.[5] Anal masturbation is a recognised form of sexual stimulation, which is in part a secondary and learnt phenomenon.[6]

In both these cases bowel control was normally established at an appropriate time and the behaviour was said to have begun in response to constipation. Only later did the patients become aware of the pleasurable component. The soiling that followed was clearly part of the difficulties that the families were having in coming to terms with adolescent separation and maturation. In a similar case soiling was used to maintain and justify a social phobia.[4] Careful direct questioning and an appraisal of the family could indicate that this phenomenon is more common than expected in children with refractory night soiling in whom there is no adequate superficial explanation.

Awareness of this may permit paediatricians to ask tactful but direct questions and subsequently to refer such young people to child psychiatrists.

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CURRENT TOPIC

Retinal haemorrhages

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Site and appearance of retinal haemorrhages

Retinal haemorrhages occur when there is extravasation of blood, either into the retina itself (intraretinal), between the retina and the retinal pigment epithelium (subretinal), or between the retina and the hyaloid face of the vitreous body (subhyaloid or preretinal). The shape and colour of the haemorrhages are determined by the level or levels of the retina affected, and they are often mixed. Often the hyaloid face ruptures and the haemorrhage spreads into the vitreous (intravitreal). Richman in 1936 classified retinal haemorrhages into four groups according to the morphological appearances,[1] and their location can be determined by their clinical appearance.

The ophthalmoscopic appearance of preretinal blood depends on its age and the size and shape of the blood filled space. Fresh preretinal blood usually looks like a dome shaped, semilunar, crescentic, or geographic accumulation of dark red blood overlying and obscuring its source. With time the same accumulation of blood can look semilunar or crescentic in shape, with a fluid level caused by gravitational settling of the formed elements. The plasma-erythrocyte interface may shift with changes in the position of the head. A faint line of residual blood usually marks the superior extent of the space originally filled with whole blood.

Intraretinal haemorrhages may be splinter shaped, flame shaped, or 'dot and blot' rounded haemorrhages. Splinter haemorrhages are small, linear, dull red, and lie superficially about the disc margin parallel to the major vessels, their shape being determined largely by the nerve fibre layer of the retina and the vessels. They may be single or multiple, and they clear rapidly.

Flame shaped haemorrhages are bright red, and lozenge shaped with a striated or serrated outline on at least one margin, and they follow the course of the retinal nerve fibre layer. They occur in the posterior pole of the fundus and are characteristically associated with disorders of the superficial radial peripapillary capillaries.

Dot and blot haemorrhages are dense, dark red, and sharply outlined. They are located within the compact middle layers of the retina and are seen in association with disorders that predominantly affect the deep retinal capillary system. Occasionally several discrete blot haemorrhages may coalesce and appear as an irregular geographic accumulation of blood.

Subretinal haemorrhages typically appear as irregular red plaques or opaque reddish circular lesions deep to the retina and retinal vessels (between the photoreceptors and pigment epithelial layer). On resolution they can result in a disturbance of the underlying retinal pigment epithelium.

Haemorrhage beneath the retinal pigment epithelial layer is usually confined, and related to a rupture (for example, trauma or pseudoxanthoma elasticum) in Bruch's membrane, which is normally adherent to it. This results in diffuse, roughly linear haemorrhages of variable—sometimes great—extent.

Haemorrhage within the choroid expands freely and forms pool like areas the ophthalmoscopic appearance of which is governed by the density of the overlying pigmentation. Generally, choroidal haemorrhages appear as dark reddish blue areas, obviously deep in the fundus, and they usually absorb leaving a normal fundus.

Some intraretinal and preretinal haemorrhages have white centres. Such lesions (or Roth's spots) are not specific for any single underlying disorder. The white centre can be focal ischaemia, an inflammatory infiltrate, a colony of infective organisms, fibrin and platelets, or an accumulation of neoplastic cells. It is easy to mistake the bright light reflex from the internal limiting membrane over the apex of a retinal haemorrhage for the small white centre of a haemorrhage.

Intravitreal haemorrhages are relatively uncommon in children; they usually resolve slowly but completely,[2] but in young children may cause amblyopia warranting early vitrectomy.

Aetiology

NEONATAL RETINAL HAEMORRHAGES

Jaeger was probably the first to have reported this condition.[3] The exact mechanism of neonatal retinal haemorrhages is not clear, but it has been suggested that blood viscosity,[4] prostaglandins in the fetal circulation,[5] and the unequal pressure distribution during birth—the sudden release of pressure with a rapid change in intracranial pressure—may be partly responsible.[6] Direct trauma is not implicated in most cases.

This usually benign form of haemorrhagic retinopathy usually presents as flame shaped or blot haemorrhages located in the posterior pole or periphery.[7] This type of haemorrhage has been a subject of a monograph[8] and the reported incidence varies enormously, from 2·6% to 50%.[4–11] The reason for this is the variable time before fundus examination after birth, the technique of examination, and whether this is histological or by direct or indirect ophthalmoscopy. Von Barsewisch pointed out that whether the examination was done by an experienced or inexperienced ophthalmologist or a paediatrician or other, significantly influenced the results[8]; the method of delivery of the baby is also important. Retinal haemorrhages occur in about one third of babies born by occipital presentation, increasing in incidence with prolonged labour and obstetric procedures,[12] and decreasing in breech presentations and birth by caesarean section.[8] Retinal haemorrhages are more common in babies of elderly primiparas,[7] and mothers with toxaemia.[13]

Retinal haemorrhages in newborn infants usually resolve within a few days.[4] Follow up studies have reported normal visual development.[14 15]

SUBARACHNOID HAEMORRHAGE

When bleeding from any cause occurs into the subarachnoid space there may be increased intracranial pressure, optic nerve sheath haemorrhage, and an increase in the pressure within the optic nerve sheath because of raised central retinal venous pressure and obstruction of the retinochoroidal anastomosis[16]; to this may be added raised central venous pressure as a result of epileptic seizures.[17] The incidence of retinal haemorrhages in subarachnoid haemorrhage is between 20%[18] and 32%,[19] and they usually occur simultaneously or are noted within a few days.[20] Streak and preretinal haemorrhages occur mainly around the optic disc and often accompany papilloedema. These haemorrhages often resolve spontaneously.[21]

Occasionally large preretinal haemorrhages may break into the vitreous (Terson's syndrome). This is often a delayed phenomenon. The pathogenesis of haemorrhages in Terson's syndrome is controversial. One view is that blood from the subarachnoid space is forced into the optic nerve sheath and penetrates the lamina cribrosa to appear within the globe.[22 23] Intraocular and optic nerve sheath haemorrhages have, however, been reported in cases of sudden intracranial hypertension in which there had been no intracranial bleeding.[24] Other authors[16 18 25] believe that intraocular haemorrhage is the result of rupture of retinal veins secondary to retinal venous hypertension, which in turn is the result of obstruction of both the central retinal vein and the retinochoroidal anastomosis.[16 18 25] For this to occur the intracranial pressure must rise much higher than it does to cause optic nerve sheath haemorrhage alone.[21]

In subdural haemorrhage the rise in intracranial pressure is less acute; they are usually post-traumatic,[26] but acute subdural haematoma has been described in association with Purtscher's retinopathy (which is normally associated with thoracic compression) in an infant with non-accidental injury,[27] and in infants with pre-existing asymptomatic chronic subdural haematoma or subdural effusion with occult craniocerebral disproportion.[28] Retinal and preretinal haemorrhages are consistently present in all infants with acute subdural haematoma.[29]

RAISED CENTRAL VENOUS PRESSURE

Raised central venous pressure from crying, seizures, or squeezing of the chest, by any mechanism where there is forced contracture of the chest against a closed or partially closed glottis,[30] may cause the so called Valsalva's haemorrhagic retinopathy,[31] which is usually associated with superficial retinal haemorrhages. Haemorrhages into all layers of the retina may be more common in non-accidental injury, at least in pathological studies.[30 32]

Retinal haemorrhages from crush injuries to the chest are usually accompanied by retinal infarcts ('cotton wool spots') and exudates in the so called Purtscher's retinopathy,[33] the mechanisms for which may be air embolism,[34] an acute rise in intraocular venous pressure, or hypoxia from angiospasm of the retina.[33]

The sudden rise in intrathoracic pressure as a result of forceful contraction of the thoracoabdominal muscles against a closed glottis causes an acute rise in central venous pressure, which in turn increases the intracranial pressure as the intracranial venous sinuses are in direct communication with the superior vena cava and there are no intervening valves in the large veins above the heart. This acute raised central venous pressure occurs with the Valsalva manoeuvre,[31] in cases of trauma when there is forced compression of the chest (usually anteroposteriorly) against a closed glottis,[35] and also in epileptic seizures,[36 37] vomiting, or spells of coughing.[37]

Appreciable rises in cerebral venous pressure (10–20 cm H_2O) have been reported[38] in neonates during episodes of crying, abdominal straining, and convulsions.[38] Values of cerebral venous pressure above 100 cm H_2O have been shown experimentally during a tonic seizure.[39] The increase in muscle tone and intrathoracic pressure makes an important contribution to this. These transient rises in cerebral venous pressure are probably responsible for the small cerebral haemorrhages seen after experimental seizures.[40] Retinal haemorrhages may occur under these circumstances but only rarely do they have more than transient effect.[37 41] The coincident rise in intraocular pressure at such times reduces the pressure difference across the vessel wall and may give a protective effect against more profuse bleeding.[37]

This mechanism could explain the occurrence of retinal haemorrhages after clumsy attempted resuscitation of infants by inexperienced adults.

NON-ACCIDENTAL INJURY

Ocular complications of non-accidental injury were first described in 1964.[42] The most common finding is retinal haemorrhage,[43 44] which occur in up to 90% of such children.[45] These haemorrhages can last for several years, in contrast to those seen at birth.[43] The cause cannot be determined by fundal examination alone or by the morphology of the retinal haemorrhages.

In non-accidental injury there are several mechanisms that cause the haemorrhage.

Raised intraocular venous pressure

This occurs by two mechanisms, often occurring together. Firstly, raised intracranial pressure is transmitted to the subarachnoid space, either through clear cerebrospinal fluid or by haemorrhage.[30] The raised optic nerve sheath pressure compresses the central retinal vein, and the chorioretinal anastomosis thus raising the pressure upstream to the capillary bed.[16]

In non-accidental injury the intraocular haemorrhages are often accompanied by intracranial haemorrhages with associated damage.[46] The severity of intraocular haemorrhage correlates with the severity of acute neurological injury.[47] Diffuse fundal impairment, vitreous haemorrhage, or large subhyaloid haemorrhages are associated with more severe acute neurological injury.[47]

The second mechanism is raised central venous pressure, as already discussed.

Rapid deceleration or cycles of rapid acceleration and deceleration

Ober and Lyle *et al* have implied that the shear forces generated by acceleration or deceleration, or both, have been a factor in the production of haemorrhages.[32 48] Duhaimi *et al*, however, have reported that the shaken baby syndrome—at least in its most severe form—is not usually caused by non-impact acceleration-deceleration forces alone.[49] The tendency for more severe retinopathy to occur in infants than in older children could be explained by clinical and experimental evidence that suggests that intraocular haemorrhages may be caused by abrupt increase in retinal venous pressure secondary to an acute rapid rise in intracranial pressure.[16 30] Infants weigh less, have a greater head size in relation to body size, and have less developed neck musculature to support the head during shaking of the thorax. These factors may contribute to the susceptibility of infants to acceleration-deceleration forces and more severe increases in retinal venous pressure.[50] Commonly, however, there are no external signs of head injury, but bilateral infantile subdural haematomas and bilateral retinal haemorrhages are present.[46] The latter are seen particularly in the posterior interhemispheric fissure, presumably as a result of tearing of the immature and fragile bridging veins. In shaken infants, retinal haemorrhages typically extend through all the layers of the retina and into the subretinal space. In Purtscher's and haemorrhagic Valsalva's retinopathy, exudates and superficial haemorrhages, respectively, are seen.[30]

BLOOD DYSCRASIAS

Blood dyscrasias with anaemia, pancytopenia, and coagulopathy may give rise to retinal haemorrhages—for example, in leukaemia and sickle cell disease.

Retinal haemorrhages occur in both acute (more common)[51] and chronic leukaemia, but their presence does not necessarily imply a grave prognosis.[52] The retinopathy is characterised by multiple intraretinal haemorrhages, subhyaloid haemorrhages, Roth's spots, exudates, and abnormalities of retinal vasculature.

In sickle cell disease retinal haemorrhages are the result of extravasation of blood through the damaged arteriolar walls after transient arteriolar occlusions and subsequent reperfusions.[53] Preretinal or intraretinal haemorrhages may evolve into retinal schisis cavities.

HYPOTENSION AND ANOXIA

Sudden reduction of systemic blood pressure because of cardiac decompensation, or traumatic shock, or treatment for arterial hypertension[54] may cause retinal and optic nerve ischaemia and haemorrhages. Sudden surgical lowering of intraocular pressure (for example, in glaucoma filtering surgery) in the presence of a healthy retinal vessel seldom produces retinal bleeding, but anoxia together with increased transmural pressure is likely to produce bleeding—for example, after difficult breech deliveries or where the cord is strangulating the neck at birth.[55]

INFECTIONS

Viral infections

In cytomegalovirus infection the retinal haemorrhages are usually flame shaped, and occur after the white lesions that look similar to 'cotton wool spots' and retinal necrosis; they may resemble retinal branch vein occlusions. The infective process spreads slowly along the course of the retinal blood vessels to encompass the entire fundus. Retinal haemorrhages are seen in acquired cytomegalovirus retinitis after cytotoxic and corticosteroid treatment in recipients of renal grafts and in patients with neoplastic disease.[56]

Other infections

Rickettsial infections,[57] subacute bacterial endocarditis, and herpes simplex are other known causes of retinal haemorrhages.

FAMILIAL RETINAL ARTERIOLAR TORTUOSITY

The progressive autosomal dominant inherited syndrome of retinal arteriolar tortuosity may be complicated by spontaneous retinal haemorrhages.[58] The retinal arteriolar tortuousity is often subtly increased during adolescence and affects small retinal arterioles, mainly in the macular area. It is easily overlooked, but even when haemorrhages affect the fovea spontaneous clearing with recovery of normal vision is the rule.

MISCELLANEOUS CAUSES AND PREDISPOSING FACTORS

Retinal diseases

Coats' disease (telangiectasis of retinal vessels), Eale's disease (retinal periphlebitis), radiation retinopathy, juvenile diabetes mellitus, hypertension, and high myopia predispose to retinal or vitreous haemorrhage.

Blood hyperviscosity

Retinal haemorrhages occur in patients with hyperviscosity of the blood such as in cystic fibrosis,[59] macroglobulinaemia,[60] cryoglobulinaemia,[61] and paraproteinaemia.[61] The mechanism by which these scattered retinal haemorrhages develop is not clear. In cystic fibrosis it has been found in patients with moderate to severe pulmonary disease.[59]

Carotid-cavernous fistula

Especially when traumatic in origin, this is considerably less common in infancy than adults.[62] The fistula produces haemodynamic changes resulting in lowered arterial pressure and raised venous pressure in the eye and orbit. The resultant reduction in perfusion pressure for a long time, with ischaemia, results in widespread intraretinal and superficial haemorrhages.[63]

Other predisposing factors

These include drugs (for example, aspirin and anticoagulants) and hypercapnia.

Conclusion

There are many causes of retinal haemorrhages in infancy, and there are several causative mechanisms. The presence, site, or physical appearance of the haemorrhages are not pathognomonic, and although their association with other clinical features could help with the differential diagnosis it is important—especially in suspected non-accidental injury—to avoid attributing causation to the presence of the haemorrhages alone.

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PERSONAL PRACTICE

Development of a psychiatric liaison service

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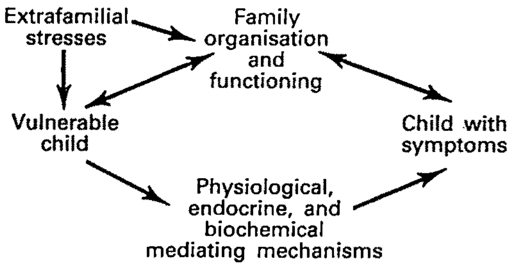
Physicians have been aware of the links between psychological processes and physical illness for centuries, and over 30 years ago Alexander described these links in a number of classical psychosomatic diseases.[1] More recently, systemic thinking has aided our understanding of the processes, and contributed to our management of both organically and non-organically induced physical complaints. The interactive and circular nature of the relationship between psyche and soma have been illustrated by Minuchin *et al* (figure).[2]

Psychological sequels of both childhood illness and admission to hospital have also been documented.[3 4] The value of a systemic approach to paediatrics—that is, seeing the child in the context of his family and social surroundings—has been highlighted by Bingley *et al.*[5]

'Liaison child psychiatry' refers to the partnership of child psychiatry, paediatrics, and other specialities concerned with children to provide integrated medical and psychological care for children. The development of liaison services has been described by a number of authors,[6–8] and different models of functioning have been proposed.[9–12] Obstacles to liaison,[13–15] and ways of overcoming them,[16 17] have also been discussed. Graham has outlined principles of referral appropriate to a child psychiatry consultation service, but has pointed out that these are less necessary when there is regular contact between specialists.[18]

Description

The Royal Free Hospital in north London is a teaching and district general hospital serving a population of approximately 100 000. It is the supraregional centre for the management of end stage renal failure and for bone marrow transplantation in children. The first child psychiatrist was appointed in 1971, but after a new consultant appointment had been made in 1984 a decision was made to concentrate the small resources of the department on paediatric and child psychiatry liaison. An awareness of a subsequent change in the pattern of referrals to the child psychiatry department following this decision led to an attempt to assess this in detail. An analysis of the work of the liaison service from mid-1984 to mid-1987 was carried out using a model similar to that used by Brown and Cooper in a study of an adult psychiatric liaison service.[19] This paper summarises some of the main findings of the analysis of referrals and considers the possible reasons for the changes. The study is described in detail elsewhere.[20]


Extrafamilial stresses
Family organisation and functioning
Vulnerable child
Child with symptoms
Physiological, endocrine, and biochemical mediating mechanisms

'Open systems' model of psychosomatic disease.[2]

Results

Most liaison referrals (n=120) were of inpatients on the paediatric ward (55%); 12·5% were inpatients on other wards. Most were made by paediatricians (66%); the others came from a wide range of hospital specialists, usually haematologists, but also neurologists, psychiatrists, surgeons, and oncologists. The bulk of referrals were either requests for help in the management of physical illness or requests for help with diagnosis in cases where no organic cause could be found for a physical complaint. The main finding of the study concerns the pattern of referrals over the three year period. Liaison referrals increased significantly in contrast to total referrals and also in contrast to the numbers of cases of self poisoning or self injury that were referred (table).

DEVELOPMENT OF THE SERVICE 1984–7

In addition to the already established referral system, a number of services and structures were developed by the child psychiatrist and the paediatricians to try and improve the service to children and their families, and the liaison between specialities and disciplines.

Psychosocial ward rounds

Until 1984 the weekly psychosocial round was not attended by a consultant paediatrician, and there was no regular time for the consultant paediatrician and child psychiatrist to meet. Since 1984 a weekly meeting of consultant child psychiatrist

Referrals to department of child psychiatry during period of study

	1984–5	*1985–6*	*1986–7*	*p Value**
Total referrals	116	104	124	NS
Liaison referrals	46	43	70	p<0·005†
Referrals for self poisoning or injury	7	14	13	NS

*Linear logistic analysis. †z=2·59.

with each consultant paediatrician was arranged after the medical round. Members of both teams are present together with nursing staff, teacher, social worker, and liaison health visitor. All contribute to a discussion about the psychosocial aspects of each case in the ward under the care of that consultant paediatrician.

Regular liaison rounds with the haematology team have also been established. The most consistently useful function of these meetings has been the sharing of information, whereby each staff member has been able to make a unique contribution to a total picture of the child and his family. An increased knowledge of the illness and its prognosis has allowed all staff to work with each patient with greater patience and understanding.

For example, many staff felt that continued attempts to sustain the life of a 7 year old girl who had had an unsuccessful bone marrow transplant and was dying were placing an intolerable stress on the child, her family, and the nursing staff. The meetings provided an opportunity to express anger about this policy, to question its validity, and to seek to modify it. Meanwhile a child psychotherapist and a social worker worked directly with the child and her family, helping them to come to terms with what was happening.

An emergency service

Each day one member of the child psychiatry team makes sure that she has some free time to be available for emergencies.

For example, early in our association, a 13 year old boy was referred, who had become panic stricken, sleepless, and disturbed several weeks after receiving a renal transplant. He was seen immediately with his mother on the ward. He had dreamed that the donor had returned to haunt him and was afraid that he would ask for his kidney to be returned. Discussion uncovered a family belief in ghosts and in heaven. The psychiatrist was able to relabel the ghost as a friendly one who was checking that his kidney was being put to good use as it was no longer of use to him, just as the boy was pleased to know that his outgrown clothes were of use to other children.

By responding rapidly and effectively we have been able to reduce patient, family, and staff anxieties and establish ourselves as useful and reliable. Feedback about our work enables ward staff to anticipate similar problems and intervene earlier to prevent the consequences.

Monthly meetings with ward staff

Regular meetings act as a forum for thinking about how to improve the ward milieu in contrast to the consideration of the needs of each patient.

Staff support

A group of student nurses meet each week with the child psychotherapist to discuss their feelings about the nature of their work on the ward—for example, their own conflicting feelings about the rigorous treatment of children with leukaemia.

Playleaders

The child psychiatrist has been responsible for the appointment, guidance, and teaching of a full time hospital play specialist.

'Ward granny' scheme

The service of a volunteer to befriend a child and his family allows the parent(s) of inpatients to take breaks to rest or to care for other family members. 'Ward grannies', who originally 'parented' children 24 hours a day, as described by Robertson, are now used less frequently than when the scheme was first introduced in 1984.[21]

Teaching of medical students

Until 1984 medical students received only four hours of teaching in child psychiatry, which has increased over the past three years to over 40 hours. Ten of these are in the paediatric block to integrate the physical and psychological aspects of illness by relating the teaching to cases and the student's personal experiences on the paediatric ward. Issues about 'death and dying,' for example, are discussed using role play as well as more conventional teaching methods.[22]

Grand round

Regular presentations at the hospital grand round were initiated by the consultant child psychiatrist. These make medical staff more aware of the services that the department can offer, and may also dispel fantasies that some may have about child psychiatrists.

For example: a 15 year old boy was referred by the oncologist, who had discovered that he was illiterate and was not attending school. At the age of 6 an operation to remove a medulloblastoma had been performed and an uncertain, but basically poor, prognosis had been given to his parents. His mother had subsequently felt unable to insist on his attending school against his will, reasoning that it was cruel to do so if he had only a short time to live. His father, who always brought him for his medical checks, was unaware of his non-attendance and the school, told of his prognosis by his mother, did not feel able to act. Liaison with the oncologist enabled the family to accept the lifting of the outdated poor prognosis. Family treatment facilitated improved communication within the family, and helped them negotiate the 5 year old sister's entry to school. We arranged for the boy to attend our hospital school after teaching him to recognise the tube station at which to alight. He learned to read and calculate in one year, left school, and is currently working as a hospital porter.

Postgraduate education

Child psychiatry academic meetings are open to paediatricians. In addition, fortnightly seminars led by members of the child psychiatry team are open to hospital staff and are regularly attended by teachers, nurses, social workers, and play specialists. Workshops about 'Working with families facing life threatening illness' and 'Working with children with physical illness' have been run for several years. Recently the child psychotherapist has considered the specific problems facing teachers in the hospital.

Publications

The child psychiatrist initiated and supervised the production of an information booklet about the child in our hospital (for parents) and contributed to one about the management of the care of dying patients (for staff). Further publications have dealt with the needs of specific groups—for example, children with blood disorders and end stage renal failure, as well as those of children on the general paediatric ward.

Prevention

Child psychiatrists now play a routine part in the assessment and management of all children admitted for bone marrow transplant or for the management of renal failure, and hopefully facilitates prevention or early detection of psychological problems.

Research

Joint research projects have been set up and have led to improved communication and mutual understanding.

Discussion

Naylor and Mattsson, in their account of the development of their own service, have emphasised the need to 'actively reach out' to paediatric colleagues,[6] but like Josse and Challener,[8] temper this with advice also to keep one's distance. The latter suggest that 'the skill comes with learning when to press on and when to hold back'.

Greene, in her consideration of the resistances to mutual collaboration, warns the child psychiatrist 'whose task is to convert disbelievers' that he may become a 'burned out missionary',[13] and indeed one of the obstacles to liaison may be the overzealous approach of colleagues who hold a specific and narrow point of view about their role. Paediatricians' beliefs about the characteristics of child psychiatrists will influence their use of—and participation in—a liaison service. Criticisms include comments about attitudes and poor communication.[15] Paediatricians and child psychiatrists work in different ways, and misunderstandings may occur about the perceived urgency of referrals or speed of response.[17] It is important that the child psychiatrist communicates clearly and effectively with all staff, and also that he is able to be available when necessary, rather than sticking to a rigid appointments system. There is little doubt that effective interventions by child psychiatrists do improve confidence, and this seems to be the case even when the intervention is relatively simple (as in the second example described). Following up an intervention with an explanation about underlying principles may result in the prevention of further psychological morbidity.

Greenberg and Rice (among others) believe that undergraduate and postgraduate medical and paramedical training can lead to increased sensitivity and awareness of emotional problems by the medical team.[16] Staff support, particularly for those facing recurrent childhood deaths, is another forum for the development of insights, both into the family's ordeal and ways of working together.[10] The psychosocial ward round is also recognised as a useful forum for the dissemination of ideas.[9]

Each area of mutual collaboration provides an opportunity for the development of the relationship between professional groups and, as noted by one of the authors in another setting, may also lead to a better defined and more realistic expectation of the service.[19]

Conclusion

In this paper we have listed a number of institutional changes that reflect the development of the child psychiatry liaison service at the Royal Free Hospital. The services and structures introduced by the child psychiatrist provide opportunities for paediatric and psychiatric staff to work together for the benefit of their patients. Regular ward rounds and educational meetings, and the provision of staff support, have led to improved relationships between the specialities. We believe that the increase in the number of liaison referrals has been a direct result of these changes. It is important to note, however, that much of the liaison work of the child psychiatry team is done 'at a distance'—that is, with staff rather than directly with patients.

We consider that the development of this child psychiatry liaison service has been both appropriate and valuable, and hope that it will lead to a reduction in the well recognised and well described sequels to both illness and hospital admission in children.

We thank the staff at the Royal Free Hospital.

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Archives of Disease in Childhood 1990; **65**: 1376–1377

Referees and staff

Our referees

Submitted manuscripts are initally seen by the editors or associate editors who then send them to one or two expert advisers for assessment. We thank the following people who kindly reviewed papers for our journal between September 1989 and September 1990. Their expertise and the time so generously given have been a major factor in maintaining high standards.

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Hodson M
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Meadows N
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Mellor D
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Morris-Jones P
Mowat A
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Phillips B
Pippard M
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Ponder B
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Staff changes

We thank Dr Richard Robinson who has retired from his post as associate editor, and was previously a member of the editorial committee, for his critical and constructive work. We thank Dr D P Addy, Dr J V Leonard, Professor E R Moxon, and Dr M J Tarlow, who have completed their periods of office as members of the editorial committee, for their conscientious and meticulous work for the journal. We welcome the following as new members of the editorial committee:

Dr T J David, senior lecturer, Booth Hall Children's Hospital, Manchester
Dr C R Kennedy, consultant paediatric neurologist, Southampton General Hospital
Dr S W Lenton, consultant community paediatrician, Bath
Dr H Marcovitch, consultant paediatrician, Horton General Hospital, Banbury
Dr P T Rudd, consultant paediatrician, Bath
Dr J E Wraith, consultant paediatrician, Willink Biochemical Genetics Unit, Manchester.

Archives of Disease in Childhood 1990; **65**: 1378

LETTERS TO THE EDITOR

Palliative care for children with cancer

Sir,—The article by Dr Goldman *et al* on palliative care for children with cancer described the work of the symptom care team in the department of haematology and oncology at the Hospital for Sick Children, Great Ormond Street.[1] However, we feel they made light of the problem of distance between the tertiary hospital and the child's home (66% more than 20 miles). Furthermore, little more than lip service was paid in the article to the expertise of the local paediatric team.

Given the right support most children can be looked after at home in the terminal stages of cancer or leukaemia. This support is very difficult to maintain at a distance, however, even with a symptom care team at the tertiary referral centre, particularly in the last days before the child dies. We would agree that it is really not realistic to expect the primary health care team, who may have had little or no experience of looking after a dying child and may not have been involved during the child's treatment programme, to give the kind of support which is required without help.

Most children with malignant disease will be diagnosed initially in the paediatric department of the local district hospital. Here we would suggest there should be a paediatrician who has a special interest in childhood malignant disease and this person should remain involved with the child's management throughout the treatment period. This can only be done with a properly organised shared care programme and this may enable some of the treatment to be given locally as well. Provided this happens the local paediatric team will be in a strong position to play a major part in the management of the terminally ill child and in supporting the family.

At the Royal Berkshire Hospital we are able to offer a domiciliary terminal care service. With help from the family's general practitioner and with our new team of paediatric community nurses we are able to give a very high measure of support in the home where it is needed. This includes a commitment to being present whenever possible when the child dies and a commitment to give ongoing support in the period after bereavement. This domiciliary service would not be possible without a shared care approach.

Shared care between the tertiary referral centre and the district paediatric department is in practice not easy to arrange. It should allow a more family orientated programme of management and better support for parents during the treatment period. We believe that more use could be made of local paediatric expertise than is suggested in the article of Goldman *et al.*

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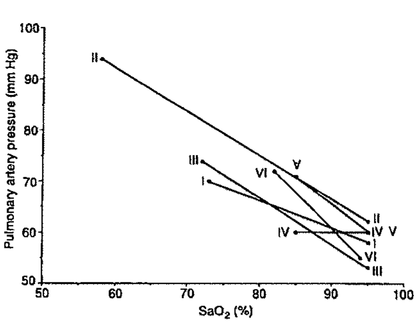
Pulmonary hypertension in bronchopulmonary dysplasia

Sir,—We read the paper by Dr Bush *et al* on changes in pulmonary circulation in severe bronchopulmonary dysplasia with great interest.[1] While we agree that some patients with bronchopulmonary dysplasia might need investigation by cardiac catheterisation, we would like to stress how much useful information can be obtained non-invasively in these patients by imaging and full Doppler ultrasound studies. In this way most congenital cardiac abnormalities can be excluded. Also when the signal of tricuspid regurgitation can be detected, a non-invasive but accurate estimation of pulmonary artery pressure can be obtained.[2] [3] It is also possible to study the reactive component of pulmonary artery pressure in bronchopulmonary dysplasia as the following case history illustrates.

Case history

A girl twin I weighing 1240 g was born at 28 weeks' gestation. She required ventilation for respiratory distress syndrome for the first eight days and a further two day period of ventilation at 4 weeks of age. A ductus arteriosus was closed with indomethacin, this being confirmed by colour Doppler flow mapping. She remained oxygen dependent with clinical and radiological evidence of severe bronchopulmonary dysplasia. Electrocardiography showed right ventricular hypertrophy, and cardiac ultrasound did not show any cardiac lesion. At 11 months she was allowed home on low flow oxygen treatment.

From the age of 10 to 16 months six Doppler ultrasound studies were performed to assess pulmonary artery pressure and to study the degree of reactivity in response to hypoxia. This was part of a larger study and informed parental consent was obtained. Pulmonary artery pressure was estimated when the patient was in oxygen (arterial oxygen saturation (SaO_2) 95%), desaturated in air (SaO_2 58–85%), and when replaced in oxygen (SaO_2 95%). The resting pulmonary artery pressure in oxygen was raised and remained fairly constant throughout the study (mean 58 mm Hg). Except in study IV at 16 months there was a clear additional reactive component when desaturation occurred (figure). Pulmonary artery pressure returned to the resting level when hypoxia was abolished (mean 57·8 mm Hg). The reactive component of pulmonary artery pressure appeared to be dependent on the degree and duration of hypoxia. At 10 months (studies I–III) reactivity was clearly visible after five minutes in air. At 16 months (study IV) no reactivity was noted after 15 minutes in air but SaO_2 fell only to 85%. Two weeks later (study V) reactivity was noted after 35 minutes in air (SaO_2 85%).



Variation in estimated pulmonary artery pressure with change in SaO_2. Six studies in patient with bronchopulmonary dysplasia.

Domiciliary oxygen was continued until 23 months of age when 24 hour monitoring by pulse oximetry showed her SaO_2 to remain >95% awake, asleep, and feeding. Her pulmonary artery pressure remained raised (58 mm Hg) but has subsequently fallen to 25 mm Hg at 2·5 years of age. There is now no evidence of right ventricular hypertrophy on electrocardiography.

The signal of tricuspid regurgitation is detected by Doppler ultrasound in most normal children but its incidence in the newborn is unknown. A clear spectral envelope must be obtained for accurate estimation of pulmonary artery pressure. We have studied eight other patients with bronchopulmonary dysplasia and detected a clear tricuspid regurgitation signal in five (62·5%). As pulmonary artery pressure can increase with activity, sedation might be required for the older infant.

In their study on eight patients with bronchopulmonary dysplasia, Bush *et al* found prostacyclin to be a better vasodilator than 100% oxygen.[1] In a similar cardiac catheterisation study on 15 patients with bronchopulmonary dysplasia, Goodman *et al* found that oxygen caused a fall in pulmonary artery pressure in all patients, the maximum fall occurring when SaO_2 was >95% but the response to a vasodilator (hydralazine) was disappointing.[4] Failure of pulmonary artery pressure to normalise with oxygen was a bad prognostic sign with 50% mortality. The patients of Bush *et al* had a very high mortality so their poor response to oxygen might well reflect the selective nature of the group.

Cardiac catheterisation is invasive. Doppler ultrasound, where possible, allows a non-invasive estimation of pulmonary artery pressure and can be used to study whether pulmonary artery pressure normalises in oxygen thereby giving prognostic information. Perhaps cardiac catheterisation and prostacyclin treatment should be directed more to the poor prognosis group where response to oxygen is poor. For the majority of patients with bronchopulmonary dysplasia oxygen, despite its inconveniences, remains the mainstay of treatment. Indeed close attention to preventing hypoxia might even abolish a relentless rise in pulmonary artery pressure. It might also help to reduce the incidence of cot death in these patients.[5]

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Qualitative expressions of probability: is there any real misunderstanding?

SIR,—I have read with great interest the paper by Shaw and Dear.[1] I think that this paper in fact addresses a very important and often neglected subject; I have however some misgivings about their results and their conclusions.

The qualitative expressions of probability used in the paper are obviously vague, but in real life they can be better defined by the context in which they are used, by the way words are uttered, by gestures, non-verbal language, prior and subsequent communications on the same subject, etc. I do not think that a physician, speaking to a mother, would say only 'Your baby is jaundiced, and will probably need phototherapy' (statement 1), and vanish. Judging an isolated statement is not representative of interpreting a real communication, so the conclusion that the use of these words can produce misunderstandings might stem from the rather artificial study context, and might not be warranted.

I am surprised that doctors differ in a systematic way from mothers in the interpretation of the qualitative expressions of probability used. These expressions are taken from everyday language, and have no specialised meaning in medicine. The differences between doctors and mothers could in part be due to artefactual factors: in particular, doctors could be more accustomed to the use of scales and to probability axioms. Using a 10 point scale as in the paper, it is natural to think that something having 0·3 (30%) probability to happen receives a '3' score, something having 0·8 probability an '8' score, etc. This requires a knowledge of the axiom that probability can assume values between 0 and 1 only, and this would not be so 'natural' among most people. In fact, Shaw and Dear report that the more educated mothers behave more similarly to doctors than the less educated mothers do. So, the problem could not lie in different interpretation of the same expressions, but rather in different ability to use the scale (that is, an artefact).

Finally, although I agree that in important decisions verbal expressions are to be avoided, I am not convinced that using numerical expressions of probability *per se* would resolve the problem. In fact, both doctors[2] and lay people[3] seem to err frequently in handling numerical estimates of probability and important principles of quantitative inference.

After reading the Shaw and Dear paper, I carried out a small experiment: I asked 12 mothers of healthy neonates in our ward to answer the following written question: 'If the probability that a neonate undergo phototherapy for jaundice is 45%, do you think it more likely that he will undergo phototherapy or not?'. I obtained only four correct answers. I'm not claiming that this small sample dismisses the use of numerical probability expressions altogether, but it raises the possibility that also in numerical communication the context may be important, and the 'message sent' may differ from the 'message received'.

So, in the absence of further evidence, I suspect that numerical expressions of probability also do not convey information unambiguously between doctors and mothers. The question remains open.

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1 Shaw NJ, Dear PRF. How do parents of babies interpret qualitative expressions of probability? *Arch Dis Child* 1990;65:520–3.
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Drs Shaw and Dear comment:
Dr Gagliardi has raised some valid points concerning our recent paper, which prompt us to make the following further observations.

The first point we wish to make is that we are in full agreement that verbal communication is a complex process which is sensitive to context and that rarely, if ever, does an entire message hang on a single word. Nevertheless, the communication of probabilistic information must inevitably make use of either quantitative or qualitative expressions of probability and we defy anyone to avoid them altogether. Our aim was to show that a single qualitative expression of probability may mean quite different things to different people and to suggest that the accuracy of communication might be increased by eliminating as far as possible these differences. We would certainly encourage the pursuit of clarity by the use of other aids to communication and of repeated explanation, although the temptation to amplify the meaning of one vague term by the addition of another should be avoided. Asking the parents to 'play back' what they have understood is a useful technique that many doctors employ.

Dr Gagliardi's second point concerned the systematic difference in the interpretation of expressions between mothers and doctors. We think that his explanation for the difference is quite plausible, but whatever the cause of the difference it is its existence that matters in the present context and it is merely another reminder of the problems inherent in the use of qualitative expressions of probability.

Dr Gagliardi's third point is supported by evidence from a small experiment. Perhaps it loses in the translation but the statement employs a relatively complex construction which could confuse. It also makes use of a percentage which we deliberately avoided because percentages are not as familiar to many people as those who use them regularly might assume. The choice of numerical representation of probability statements is very important and our experience is that scores are more widely comprehended than percentages. If Dr Gagliardi had presented his subjects with the following statement he would surely have reported a higher level of comprehension: 'Out of 20 jaundiced babies, nine will need treatment with phototherapy but the remaining 11 will not'.

Serum immunoglobulins in acute lymphoblastic leukaemia

SIR,—Serum immunoglobulin concentrations in normal children increase with age, as Jackson *et al* have confirmed.[1] Many investigators of the immune status of children with acute lymphoblastic leukaemia have reported low concentrations of immunoglobulins after treatment has started.[2–4] Attention has been drawn to the 'masking' effect of the intrinsic variation in concentrations with age when interpreting results from groups of these children.[4] Jackson *et al*, in the second of their papers on antibodies to endotoxin core glycolipid argue: 'Furthermore, total IgG concentrations were not significantly reduced in children with acute lymphoblastic leukaemia, suggesting that the reduction in specific antibody was not a reflection of the total immunoglobulin concentrations'.[5] From the preceding sentences of that paragraph, this statement appears to refer specifically to children with acute lymphoblastic leukaemia on treatment. However their own data suggest that IgG concentrations during continuing treatment are lower than those in controls ($p<0{\cdot}05$; their analysis). Age related data might show an even greater discrepancy.

As to the importance of anti core glycolipid antibody titres before treatment started, they use in their argument the observation that total IgG concentrations are not significantly reduced yet, on the other hand, allude to abnormally low anti core glycolipid antibody titres at diagnosis despite the lack of a significant difference in these specific antibodies between patients with acute lymphoblastic leukaemia and controls. This is not meant necessarily to detract from their hypothesis that pre-existing and/or treatment induced abnormalities of the immune system may result in abnormally low titres of anti core glycolipid antibodies in some patients; but could they clarify their argument?

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Drs Jackson, Parton, Shortland et al comment:
We acknowledge the queries raised in Dr Reid's letter. First, while it is true that the total IgG fell to just significant concentrations in children with acute lymphoblastic leukaemia on maintenance chemotherapy, the total IgG concentration in children with acute lymphoblastic leukaemia as a whole were not significantly decreased. However, the specific antiendotoxin core glycolipid IgG was significantly reduced in this group of patients as a whole, and more significantly reduced in those on maintenance chemotherapy. Indeed, we also found total IgG was the least affected immunoglobulin class in this group of patients. Therefore we feel that these antiendotoxin antibodies are specifically depressed in children with acute lymphoblastic leukaemia.

Secondly, although there are variations in publications of total immunoglobulin concentrations in children with acute lymphoblastic leukaemia,[1–3] the specific anti core glycolipid antibodies were consistently reduced in our study at diagnosis. Furthermore, concentrations of anticore glycolipid antibodies at diagnosis correlated significantly with the number of pyrexial episodes experienced during subsequent treatment. Such a relationship could not be detected for total immunoglobulins.

We accept that there are large variations in the distribution of immunoglobulins in children suffering from acute leukaemia, but feel our data suggests a functional importance of specific anti core glycolipid antibodies in this disease.

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Relative occurrence of neuroblastoma and Wilms' tumour in ethnic subgroups in the West Midlands Health Authority Region

Sɪʀ,—There have been several reports commenting on the apparent rarity or indeed absence of neuroblastoma cases in Zaire and surrounding African countries.[1–4]

This discussion has importance not only in assessing the aetiological significance of the observation for the countries concerned but also for studies of the relative rates of cancers in immigrant populations of other countries. Such studies have been revealing in adult cancers—for example, Japanese immigrants to the USA now show the spectrum of disease endemic to the American lifestyle rather than maintaining the pattern seen in their native country.[5] The implication of these studies is that, in adult cancers, most of which are carcinomas, environmental as opposed to genetic factors are more important in the aetiology.

Similar studies are rare in paediatric 'solid' tumours but are important because childhood tumours (being typically embryonal or tumours of the central nervous system, with carcinomas occurring as only 3% of cases) may have different causes.

We have reviewed all cases of neuroblastoma and Wilms' tumour (252 and 175 respectively) occurring in the West Midlands Health Authority Region (WMHAR) during the period 1957–86, as part of the data collection of the West Midlands Regional Children's Tumour Research Group (WMRCTRG). All cases are subjected to review of the histology material by specialist paediatric pathologists in order to confirm the diagnosis.

Included in this review is an investigation of the ethnic origin of the patients. The WMHAR contains a relatively large number of immigrants of Afro-Caribbean and Asian extraction, although exact childhood population figures are not available. Confirmation of ethnic group of each patient was obtained from the hospital casenotes or by communication with the general practitioner. Where these sources were unhelpful, examination of the family name of the patient denoted Asian origin and the presence of a sickle cell test provided further evidence of Afro-Caribbean origin.

Relative occurrence of neuroblastoma and Wilms' tumour by ethnic group in the WMHAR

	White	*Afro-Caribbean*	*Asian*	*Other**	*Total*
Neuroblastoma	236	2	10	4	252
Wilms' tumour	161	8	5	1	175

*Other=Chinese/Japanese/mixed.
Tests of proportions: (1) Afro-Caribbean for neuroblastoma compared with Afro-Caribbean for Wilms' tumour: $p<0\cdot01$; and (2) Asian for neuroblastoma compared with Asian for Wilms' tumour: $p>0\cdot05$.

The results shown in the table show that, in our 30 year series, neuroblastoma was indeed rare in Afro-Caribbeans with only two cases seen (0·8%). By comparison, neuroblastoma was proportionally five times more common in the Asian group (4·0%). Furthermore, during the same time period there were eight cases (4·6%) of Wilms' tumour in Afro-Caribbean children, proportionally slightly more than were seen in Asian children (2·9%). The results for Wilms' tumour may be seen as a control in that they confirm that cases diagnosed in black children are successfully ascertained by the Registry.

As insufficient population data are available for children by ethnic group breakdown, we are limited to expressing these results as a proportion. This difficulty in producing specific population standardised data is thus not only a problem for Third World countries but also for UK registries.

The fact that neuroblastoma is rare in our series of Afro-Caribbean children resident in the West Midlands suggests that genetic rather than environmental factors may be contributing to its aetiology. However, further, more detailed comparisons will depend upon the provision of accurate data such as that of Dr Massabi *et al*,[1] and on the availability of more specific population data.

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Reduced sweating in Laron's dwarfism

Sɪʀ,—We have recently shown that adult patients with growth hormone deficiency have a reduced sweat secretion rate when compared with age matched controls.[1] Their sweating was correlated to the serum concentration of insulin like growth factor I (IGF-1).[1] The question remains, however, as to whether growth hormone itself directly influences the sweat glands, or whether its action is mediated through IGF-1.

We have examined sweating in a 22 year old man with Laron's dwarfism (height: 124·2 cm, Tanner stage of puberty 3). He presented with highly raised serum growth hormone values (86 μg/l) and unmeasurable serum IFG-1. He had a sweat secretion rate of 24·9 mg/30 minutes as measured with the pilocarpine iontophoresis test.[2] After treatment with subcutaneous injections of biosynthetic growth hormone for four days (3 IU/day, Genotropin, KabiVitrum) the measurement of serum IGF-1 and the sweat test were repeated. IGF-1 was still undetectable and the sweat secretion rate did not increase (23·6 mg/30 minutes). Both sweat secretion values are much lower than the lowest reference value for a group of 18 to 40 year old healthy men (median: 112·7, range: 59·2–259·9 mg/30 minutes, n=17) as well as for a group of healthy boys in puberty (median: 110·3, range: 49·3–202·4 mg/30 minutes, n=39).

Thus our observation is in agreement with the hypothesis that the effect of growth hormone on sweating is mediated through IGF-1.

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This study was supported by the Danish Medical Research Council grant No 12-9361.

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BOOK REVIEWS

The Diagnosis and Management of Paediatric Respiratory Disease. By Robert Dinwiddie. (Pp 312; £24·95 hardback.) Churchill Livingstone, 1990. ISBN 0–443–02744–7.

The author's declared aims in compiling this new textbook on paediatric respiratory disorders are to give a basic overview of the subject, to highlight recent advances, and to give guidance on further reading. The book is directed at junior paediatricians and interested general practitioners. How well does Dr Dinwiddie succeed in his objectives?

Of the 14 chapters, three are by colleagues who have worked with the author at the Hospital for Sick Children, Great Ormond Street. The first sections deal with the development and function of the respiratory system, and are followed by chapters on neonatal respiratory disorders, and congenital anomalies. Respiratory infections, asthma, cystic fibrosis, aspiration, ear, nose, and throat problems, the lung in immune disease, and rare lung disorders are also covered. The final sections deal with radiology and artificial ventilation.

Dr Dinwiddie certainly achieves his aim of providing an overview of respiratory illness in children. The text is well referenced for those wishing to read in further depth. However, in giving practical advice on the assessment and management of specific diseases, he is less consistently successful. The chapters on cystic fibrosis, mechanical ventilation, and neonatal disorders are excellent, but in other sections, notably those on the management of asthma and pneumonia, the important messages are concealed by too many unhelpful caveats such as 'if necessary', 'not infrequently', 'when appropriate', or 'in the usual way'. The junior doctor who wants to know which antibiotic to give to the child with pneumonia, or when to start prophylactic treatment, or which drug to use by which device in the young asthmatic, will have difficulty finding clear guidance in this book.

The emphasis on certain rare disorders at the expense of other, more common illnesses, often seems to reflect the interests of the authors, and the selective nature of referrals to the Hospital for Sick Children, rather than the importance of the disorder. For example, the description of *Pneumocystis carinii* pneumonia, an increasingly important but uncommon infection, covers two pages, whereas the management of the child with recurrent cough, one of the commonest reasons for children being referred to the outpatient clinic, merits only 19 lines of text, together with a table listing the causes. Some important clinical problems, such as allergic rhinitis, apnoeic/cyanotic attacks in infancy, and psychogenic cough, are not covered at all. In many patients with respiratory disease, a careful history and clinical examination will lead to the diagnosis. I am disappointed that a book aimed at junior doctors does not have a specific section on the history and interpretation of the physical signs of respiratory disease.

Despite these criticisms, this book will be a useful addition to the library. It will be particularly valuable for those studying for postgraduate examinations and as a source of references. It is remarkably good value for a hardback text.

J M COURIEL
Consultant paediatrician

Continuities of Deprivation? Edited by I Kolvin, F Miller, D Scott, S Gatzanis, M Fleeting. (Pp 408; £38·50 hardback.) Gower Publishing Company Limited, 1990. ISBN 0–566–05799–9.

A speech by Keith Joseph seems an unlikely starting point for a study on deprivation but it's true. It was in 1972 that Sir Keith, speaking to the Pre-School Playgroups Association, called for research into the mechanisms of the 'cycle of deprivation'; a surprising call for a Thatcherite minister, but then, that was in a bygone era.

The '1000 families' in Newcastle upon Tyne seemed an ideal source of information to study the intergenerational links in deprivation, and this is what Kolvin and colleagues have given us in 400 dense pages which would benefit from some colour to bring them to life. The subject under study could hardly be more important and there is a wealth of resource material to argue for political and social change, though few clear messages for action seem to emerge from its pages.

It was a remarkable piece of work to carry out a 33 year follow up on a sample of the 847 families remaining in the city in 1952, from the original birth cohort of May to June 1947. Six criteria of deprivation were developed for the 1952 population, and seven for the 284 interviewed in 1980. Schools were visited and each child was measured and tested (as the earlier generation had been in 1962). I searched hard to find the authors' definition of deprivation: an overused term, and one which is not well liked by the people who suffer it. I quite like Keith Joseph's definition 'circumstances which prevent people developing their potential'. I had reached p330 before I could find the present authors' definition: 'any circumstance which was considered socially or psychologically undesirable in itself for normal family life'.

Six deprivational criteria were identified in 1952 and the seventh was added in 1980: family/marital disruption, parental illness, poor physical care, social dependence, housing (overcrowding), poor mothering, and educational insufficiency. Are these the right criteria and does each carry the same weight? One could argue till doomsday and the only ones I question are 'poor physical care' and 'poor mothering'. No definition is given. Their presence must be a judgment, perhaps influenced by the other criteria? This is an important point because the authors group the cohort into 'no deprivation', 'moderate deprivation' (one or two criteria), and 'multiply deprived' (three or more criteria). In 1952 the percentage in each category was 59%, 29%, and 34% respectively. In 1980 figures for slightly differently defined categories were 28%, 49%, and 22%. Hereafter, interpretation stops being simple and all I can do is extract a few takeaway messages from this complex and difficult to read book:

Educational insufficiency was common in all groups but especially the deprived (45% of the total and 20% of non-deprived in 1980: a remarkable figure).

The deprived group were characterised by frequent absences of fathers.

Overcrowding is one of the few criteria which has distinctively improved since 1952.

The deprived showed both upward and downward mobility.

More non-deprived children attended preschool education (is this motivation or availability?).

One in three of the multiply deprived contemplated suicide.

Women carry most of the burden of family deprivation.

Half the families changed their category between 1952 and 1980 (so it *is* possible to move out of deprivation).

Movement into deprivation was chiefly due to educational insufficiency, marital disruption, and parental illness.

Key protective factors against deprivation recurring in the second generation are higher intelligence, a successful school career, adequate vocational training, and a stable marriage.

Youth clubs may protect against a criminal career.

Multiply deprived women who 'moved up' married brighter spouses than themselves.

The report is short on recommendations for action by any of the 'caring services': a pity, as a political speech had started it off.

An important feature which is lacking in the book is an economic analysis of the family's lives, because to me, shortage of money is a paramount 'pivotal' point for deprivation. A personal view is that the main 'solutions' to deprivation must come from social/political change and a greater investment in education. For paediatricians, it is enough to know that deprivation in a second generation is by no means inevitable.

This study provides data which should be included in our textbooks and our training.

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Consultant community paediatrician

Lovell and Winter's Pediatric Orthopedics. 3rd Ed. Edited by Raymond T Morrisy. (Pp 1280; $195 hardback.) J B Lippincott Company, 1989. ISBN 0–397–50914–6.

This is an excellent and comprehensive text, which is now established as one of the leading and authoritative books on paediatric orthopaedics. In this third edition, there is a large increase in number of authors and two new chapters on imaging and sports medicine. In addition, the improved layout and text make it a very easy reference book to use.

There are two volumes. The first addresses generalised disorders affecting children and includes excellent chapters on juvenile rheumatoid arthritis, neuromuscular disorders, and cerebral palsy. Each section gives information of interest to any specialist managing these disorders, but they are particularly useful to the orthopaedic surgeon, whether in training or with an established paediatric practice.

The second volume addresses specific areas of the body; the foot receiving much more extensive attention than in previous editions, with six chapters devoted to it. These chapters give an excellent review of the various deformities affecting the foot, without giving the overriding impression that all deformities need to be corrected surgically, and quite correctly pointing out some of the problems that surgery can impose.

There is also an excellent section on leg length discrepancy which includes the latest techniques in this rapidly evolving field, although details are a little sketchy.

This book is aimed at both the trainee surgeon and the established orthopaedic surgeon and neither group will be disappointed by having it in their library.

LAWRENCE S FREEDMAN
Consultant orthopaedic surgeon

Neonatal Surgery. 3rd Ed. Edited by James Lister and Irene M Irving. (Pp 733; £135 hardback.) Butterworth Scientific Ltd, 1990. ISBN 0–407–01490–X.

I enjoyed reviewing this book. If not already available in your departmental library or special care baby unit, the deficiency should be remedied. If it is available it is likely to be the second edition (1978), and should be replaced by this, the third (1990).

There have been impressive advances in the surgical care of neonates in the past 20 years, often made possible by the expertise of neonatologists, and specialist anaesthetists, as acknowledged by the authors. If any questions remain of the value, indeed necessity, of specialised units for the surgical treatment of the newborn they are answered in this book, which incidentally, reinforces the findings of the report of the National Confidential Enquiry into Perioperative Deaths published in June of this year.

The experience of the staff at The Royal Liverpool Children's Hospital (Alder Hey), in providing a comprehensive regional service for primary through to tertiary referral, for a population of some three million, is unlikely to be matched in this country. This experience, presented in a pleasing and easily readable manner, does them and the publishers credit.

The opening chapter, of eight, by Peter Rickham, one of the authors of the first edition in 1969, provides a thoughtful update on the question of the ethics of surgery in newborn infants. Other chapters include a discussion of the impact of antenatal diagnosis in surgical practice, and the problems presented by the increasing number of low birthweight babies requiring surgery. This section should perhaps have also dealt with another recent change: the necessity for surgical audit with its prerequisite for the accurate collection of clinical data, and the means of achieving this. No doubt the fourth edition will have to comment on these matters, giving perhaps details of costs and departmental budgeting!

After part II which deals with trauma, tumour and twins, the remaining parts provide a systematic description of surgical disorders with historical details and descriptions of pathology, diagnosis and treatment. It is unnecessary to comment on these individually, but I particularly noted the sections on oesophageal atresia and Hirschsprung's disease.

Detailed criticism can always be made in such a review. In looking through the index I would have liked to have found it easier to be guided about postoperative intestinal obstruction, a not uncommon and potentially dangerous condition which may pose difficult diagnostic problems. In the chapter dealing with intestinal surgery the importance of regimens of preoperative and postoperative antibiotic treatment, which have reduced morbidity and mortality so much in recent years, could have been stressed more clearly, at least by reference to the appropriate section of the book. However, these are small points.

This book is essential reading for paediatric surgical trainees faced with the intercollegiate examination. It would also be enjoyed by others who care for infants and children, including general surgeons whose practice involves paediatric surgery.

Congratulations are in order!

MALCOLM GOUGH
Consultant surgeon

Textbook of Pediatric Rheumatology. 2nd Ed. Edited by James T Cassidy, Ross E Petty. (Pp 620; £65 hardback.) Churchill Livingstone, 1990. ISBN 0–443–08640–0.

Over the past three years I have inquired from more than 100 candidates, trained to take the MRCP examination in paediatrics, 'You have heard of Still's Disease but who was Still?' No one knew much about him and indeed only two had any idea who he was. Answers ranged from a German physician of the 18th Century to a doctor from New York. Good heavens people!! He was, among other things, the first president of the British Paediatric Association, the first Professor of Paediatrics in the UK and what's more he was paediatrician to the present Queen when she was Princess Elizabeth, hardly a man of great antiquity. He also produced the first English description of arthritis in children in 1897, in a paper reproduced in the *Archives* in 1941 and well worth reading. He described 'his disease' while a resident at Great Ormond Street, surely a lesson for todays' trainees. Well, if my MRCP candidates didn't know who Still was, does this new American textbook of paediatric rheumatology pass the test? Being an American book, I wouldn't have been surprised if it had scarcely mentioned anything that happened on this side of the Atlantic. However, I was delighted to see Still appearing in the index as well as due credit being given him, and more latterly, the Taplow team of Bywaters and Ansell, for their substantial contributions to paediatric rheumatology.

Is this a book that every paediatrician should have on his bookshelf, to be referred to probably infrequently when he has a child with an unusual arthritic problem? My answer would be undoubtedly yes, in that it provides a comprehensive and up to date account of rheumatic and allied disorders in children. It not only covers true arthritis, but also includes problems of non-rheumatic origin, for example, aches and pains, skeletal disorders, and hypermobility. The black and white illustrations are excellent as evidenced by a very convincing picture of a 'Still's rash'. Incidentally the rash is the only common systemic feature which Still did not include in his description. The illustrations of nailfold capillary changes in dermatomyositis will make you reach for your magnifying lens next time you suspect this disease. There is some confusion for the European reader in that the Americans insist on lumping together all chronic arthritis in children as juvenile rheumatoid arthritis (JRA) as opposed to this side of the Atlantic where we reserve this term for those with a positive rheumatoid factor and call the rest juvenile chronic arthritis (JCA), but they do at least acknowledge the difference of opinion. The book deals comprehensively with all of the common, and not so common conditions that the general paediatrician is likely to encounter. Also included are some rarities of which you may not have heard, for example, the intriguingly named 'streaking leucocyte syndrome' and 'Kashim-Beck (Urov) disease'. My only criticism of this otherwise excellent book is that it doesn't give sufficient details of non-medical methods of management. If you want to know which drug to give for each disease and its potential effects and side effects then you will find it here. However, although there are 18 pages devoted to 'treatment' of JRA only one and a half of these relate to physiotherapy. The correct use of physical methods of treatment has done more to prevent long term disability than any other form of treatment and it is a pity that there was not more emphasis on this. This is a useful book for any general paediatrician and an essential one for those specialising in paediatric rheumatology. It will also be useful for other disciplines, and I hope that orthopaedic surgeons will heed the message that synovial membrane biopsy should *not* be done unless an alternative diagnosis, for example, tuberculosis, is being seriously considered.

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The Development of Mature Walking. Edited by David H Sutherland, Richard A Olshen, Edmund N Biden, Marilynn P Wyatt. (Pp 227; £24 hardback.) MacKeith Press (Blackwell Scientific Publications Ltd.). 1988. ISBN 0–632–01902–6.

Clinical observation of children's gait characteristics, though important, has proved to be an insufficiently reliable basis for decisions about orthopaedic surgery or evaluation of treatment. With a roll of lining paper and a pot of ink to daub on the soles of the feet or a sprinkling of chalk dust on the floor, it is possible to measure width of the base, stride length, and angle of the feet to the plane of walking, and the area of the foot in contact with the floor. With a stopwatch, speed can be recorded and cadence counted.

The motion analysis laboratory at the children's hospital, San Diego, offers a cleaner high tech method involving cine film force measurement, electromyography, computer analysis, and advanced statistical treatment. Four hundred and forty nine observations of 309 normal children from onset of walking to 7 years are reported in this classic, sophisticated monograph. The results are a landmark in the science of motion analysis and of use to those whose eyes glaze at the prospect of Fourier analysis and 'bootstrap' computer analysis.

The number of paediatricians who will understand the chapter on the mathematics of modelling and prediction regions could be counted on the fingers. Those who do not know the difference between step length and stride length will find 60 consecutive pages of four waveform figures each, rather taxing. None the less, fundamental normal data are presented (for example, on stride length, cadence, and velocity), in ways which are of interest to those still restricted to 'stopwatch and woad'.

As a source of reference on the normal range of ability, to walk on toes or heels, to run, balance, hop, and develop dominance, it is useful to child development services. The data did not require an elaborate gait laboratory but allow cross referencing with other studies.

It is a book to buy for treatment course libraries, physical education departments, thinking and committed orthopods, and academic libraries.

IAN McKINLAY
Senior lecturer (community child health)

Colour Atlas of Paediatric Haematology. 2nd Ed. Edited by Ian M Hann, Brian D Lake, Jon Pritchard, John Lilleyman. (Pp 148; £60·00 hardback.) Oxford Medical Publications, 1990. ISBN 0–19–261893–8.

Those who criticise colour atlases as being full of pictures but of little substance would do a great injustice to this guide to paediatric haematology. The colour photographs of blood and bone marrow are quite spectacular and full of detail, and the text, although necessarily brief, is concise and authoritative.

The authors ensure that the normal appearances of blood and bone marrow are properly described before turning their attentions to paediatric haematological disorders. I was pleased to see that the section on neonatal and perinatal disorders included blood films of sick infants without primary haematological conditions, as these can be most misleading to the less experienced observer.

In this second edition of the atlas the authors have added a good deal of new material, especially in sections dealing with acute leukaemia, perinatal and storage disorders. This book is intended as an 'aide memoire' for haematological and technical staff in hospital laboratories who are not working exclusively in the field of paediatric haematology. It may also, however, be of interest to many general paediatricians wishing to know more about the haematological aspects of the problems of children in their care. I have no doubt that this book, with its well deserved continuing popularity, will adorn the shelves of many haematology and paediatric departments over the next few years.

C L NEWMAN
Consultant paediatrician

NAWCH Quality Review—Setting Standards for Children in Health Care. Christine Hogg. (Pp 80; £14·95 paperback.) NAWCH, 1989. ISBN 0904076–06–07.

The National Association for the Welfare of Children in Hospital (NAWCH) *Charter for Children in Hospital*, published in 1985, provided us with a clear comprehensive statement of children's needs when in hospital care, whether in Manchester or Mukka Flugga. Now comes son of NAWCH, or the *NAWCH Quality Review*, which itself emerged from the *Quality Checklist for Caring for Children in Hospital* published in 1988.

Its stated aim is to provide a tool to look at the 'total experience' of the child while in health care: as an outpatient, in operating theatres and radiography departments, as well as in the hospital wards where children are looked after. All the staff the children encounter—porters, receptionists, nurses, or doctors—are also included. By doing this, a profile of the services provided in a district can be drawn up and can act as the basis of a dialogue between clinical staff and managers about the service for which they are mutually responsible.

The first part of the book outlines the rationale behind current policies relating to the care of children. It then proceeds to give detailed quality checklists under separate headings in two main categories—policy and planning and service provision for children. Examples of the first are on district health authority policy and planning and nursing policy. In the second category are included checklists for outpatient clinics, diagnostic and support services, and accident and emergency departments. To round off this section there are two questionnaires for parents.

Personal experience of using this document in an average sized NHS district over the past nine months has shown its usefulness in compiling a picture of the service drawn from the responses of a wide range of staff. It clearly showed areas of strength and weakness and areas of confusion between different members and groups of staff, and had a remarkable ability to clarify issues for dialogue with managers of the service. It was readily accepted by the district general manager and district health authority as the basis for quality assessment and its recognition in the drawing up of service contracts. Finally it was helpful as a tool to discuss problems in common with members of staff who deal with children as only a part of their overall work, for example, anaesthetists, outpatient nurses, and ear, nose, and throat surgeons. It provides a basis for discussion rather than a threatening confrontation over issues that arise.

In the current climate of changes in the NHS, this book provides an invaluable guide to those working with children. Each children's department should purchase at least two copies so that it is readily available for the use of both clinical staff and managers. I await with interest the production of a similar volume dealing with community child health.

RICHARD J PURVIS
Consultant paediatrician

Pediatric Hepatology. Edited by William F Balistreri, J Thomas Stocker. (Pp 498; £100 hardback.) Hemisphere Publishing Corporation, 1990. ISBN 0–89116–738-2.

This book is based on a seminar on paediatric hepatobiliary disease, which is the third of a series of seminars on paediatric disease held at The Gant in Aspen, Colorado. It is greatly to the credit of our American colleagues that they managed to tear themselves away from the ski slopes long enough to produce this excellent book, which provides an up to date view on many aspects of paediatric liver disease. The contributors include paediatricians, pathologists, and basic scientists and are drawn from many centres in the United States, notably the Children's Hospital Medical Center, Cincinnati, the Armed Forces Institute of Pathology, Washington, and the University of Colorado, Denver.

It does not attempt to be a comprehensive textbook but provides recent information and an insight into many enigmatic and difficult topics in paediatric liver disease. It is very definitely a book for specialists or subspecialists who have an interest in liver disease and its associated problems. I would think its general appeal is limited as it is not comprehensive enough to use as a reference text for general paediatricians but would be helpful for trainee paediatricians researching a specific problem.

The topics include many of the 'usual' problems such as infantile cholangiopathy, biliary atresia, total parenteral nutrition associated cholestasis, an update on α_1 antitrypsin deficiency, and an obligatory, but rather brief, chapter on liver transplantation.

I was interested by the attempt to unravel the mysteries of Reye's syndrome and its metabolic mimickers (William F Balistreri), and a comprehensive and well written chapter on systemic disorders associated with hepatobiliary dysfunction (Basil J Zitelli).

The chapter on fulminant hepatic failure was well discussed (Ronald Sokol), and was one of the few chapters with a good guide to the management of this fatal condition. Less impressive were the chapters on acute and chronic hepatitis, which were rather mundane and out of date with little discussion of the new and exciting advances in autoimmune hepatitis, hepatitis C, antiviral treatment, and vaccine prevention of this illness. The chapter on liver transplantation was too brief and not sufficiently up to date for the readership of experts for whom the book is intended.

There is a practical section on the pathology of inherited metabolic disorders (Kamal G Ishak), with an excellent account of appropriate methodology. However, the large number of metabolic diseases included meant that the description of their pathological changes was less helpful to an expert but useful as a general screening guide for non-specialists.

I found the chapters on classification of hepatic tumours (J T Stocker) and hepatic allograft pathology after transplant (Rodney S Markin) very clear with helpful summaries of these difficult areas.

There is much emphasis on the difficulties of making a diagnosis in many curious conditions. Disappointingly, there is very little practical help given in the management of these disorders. I was particularly disappointed to find that there is no mention of the psychosocial aspects of liver disease and the necessity to provide support for families of children with such devastating illnesses.

As in most published seminars, the chapters tend to read like scripts for a lecture, but despite this drawback the topics are well reviewed and well illustrated and would be most helpful to paediatricians in training, or practising in gastroenterology, hepatology, or metabolic disease.

In summary this book attempts to bring up to date the less well known areas of paediatric liver disease, and is fascinating reading for the select group of paediatricians concerned with these problems, but it will not be of interest to the general paediatrician and neither is it meant to be.

DEIRDRE KELLY
Consultant paediatric hepatologist

Paediatric Rheumatology Update. Edited by Patricia Woo, Patience H White, Barbara M Ansell. (Pp 247; £30 hardback.) Oxford University Press, 1990. ISBN 0–19–261860-1.

This book aims to present current thinking, both in management and research in the field of paediatric rheumatology. It is based on an international symposium that commemorated the retirement of Dr Barbara Ansell, and is not aiming to be an up to date comprehensive textbook but to focus upon changing knowledge, ideas, and practice. I feel that I have learnt more from this book than having attended the meeting.

The book is divided into three parts: firstly, juvenile chronic arthritis, secondly, the differential diagnosis of juvenile chronic arthritis and thirdly, the rarer connective tissue diseases. Some aspects of paediatric rheumatology, such as immunogenetic aspects, have changed greatly over the past 10 years and were comprehensively covered. They provided good resumes with numerous recent references. Other topics have changed little in recent years and therefore some sections did not add much that was new.

I realise that there was international authorship but I was slightly irritated by the inconsistent use of JCA/JA/JRA terminology. The difference in their uses in Europe, America, and worldwide was explained but I would still have preferred consistent use of one terminology throughout the book.

This book has a place, not least as a useful source of current references, and I am sure it will be bought by all those who attended the meeting as well as those who were unfortunate to miss it. The book highlights the state of the art at the end of the era led by Dr Ansell's enthusiasm.

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VOLUME 65 · AUTHOR INDEX

Addison G M Urinary growth hormone excretion: correspondence **811**
  see also Price D A *et al*
Addy D P Phenobarbitone and febrile convulsions: annotation **921**
  see also Andrews R *et al*
Ades A E Evaluating screening tests and screening programmes: current topic **792**
  see also Smith I *et al*
Adjrad L *see* de Montalembert M *et al*
Agnarsson U, Warde C, McCarthy G and Evans N Perianal appearances associated with constipation **1231**
Ahmed F, Ellis J, Murphy J, Wootton S and Jackson A A Excessive faecal losses of vitamin A (retinol) in cystic fibrosis **589**
Ahmed M L, Yudkin P L, Macfarlane J A, McPherson K and Dunger D B Are measurements of height made by health visitors sufficiently accurate for routine screening of growth? **1345**
Aitchison T *see* Hudson I *et al*
Akbar M S *see* Roy S K *et al*
Alam A N *see* Roy S K *et al*
Alani S M *see* Wraith J E and Alani S M
Alberman E *see* Evans P M *et al*
Alberman E D *see* Pharoah P O D and Alberman E D
Alexander I S *see* Chidiac P and Alexander I S
Allan L D *see* Paladini D *et al*
Almond G *see* Holmström G *et al*
Alroomi L G *see* Macdonald P D *et al*
Altman D G *see* Earley A *et al*
Amirav I Increases in plasma concentrations of a prostaglandin metabolite in acute airway obstruction: correspondence **559**
Anagnostakis D *see* Messaritakis J *et al*
Anderson E S, Petersen S A and Wailoo M P Factors influencing the body temperature of 3–4 month old infants at home during the day **1308**
  Use of thermographic imaging to study babies sleeping at home: **1266**
Anderson H R *see* Mitchell E A and Anderson H R
Anderson J M *see* Preece P M *et al*
Andrews R, Morgan J D, Addy D P and McNeish A S Understanding non-attendance in outpatient paediatric clinics **192**
Angeleri E M T *see* Tam P K H and Angeleri E M T
Anjos R Dos *see* Dos Anjos R
Annerén G, Magnusson C G M and Nordvall S L Increase in serum concentrations of IgG_2 and IgG_4 by selenium supplementation in children with Down's syndrome **1353**
Ansari B M *see* Jenkins H R and Ansari B M
Appleton R E, Farrell K, Zaide J and Rogers P Decline in head growth and cognitive impairment in survivors of acute lymphoblastic leukaemia **530**
  Lee R E J and Hey E N Neurodevelopmental outcome of transient neonatal intracerebral echodensities **27** *fn*
  see also Wilson D I *et al*
Appleyard W J Children's services in the new NHS—a struggle for survival?: current problems **635**
Archer L N J *see* Evans N J and Archer L N J
Ardjoun F Z *see* de Montalembert M *et al*
Arends J W *see* van der Meer S B *et al*
Asen K Paradoxical approach to the management of faecal incontinence in normal children: commentary **600**
Ashmore S P *see* Caswell S J *et al*
Ashurst H *see* Johnson A and Ashurst H
  Johnson A *et al*
Asthana J C, Sinha S, Haslam J S and Kingston H M Survey of adolescents with severe intellectual handicap **1133**
Austin R P and Nibhrolchain C The five year school medical—time for a change: correspondence **912**
Aylett S E, Williams A F, Bevan D H and Holmes S J K The Kasabach-Merritt syndrome: treatment with intermittent pneumatic compression: **790**
Aynsley-Green A *see* Murphy M S *et al*
  Waterston A J R *et al*
Aziz K M A *see* Briend A *et al*
Azzopardi D *see* Midgley P C *et al*

Bailey C M *see* Morrissey M S C and Bailey C M
Bailey B J R *see* Voss L D *et al*
Bain H H *see* Wilson D I *et al*
Bain M *see* Verber I G and Bain M
Baker B A *see* Lucas A *et al*
Baker M *see* Rayner R J *et al*
Baldwin M *see* Watkin P M *et al*
Ball P A *see* Puntis J W L *et al*
Balloch A *see* Sennhauser F H *et al*
Bamford J M *see* Scanlon P E and Bamford J M
Bamford M F *see* Lucas A *et al*
Banks J H *see* Porter J D H *et al*
Bannon M J Screening infants for hearing loss: correspondence **158**
  and Carter Y H Early identification of hearing loss: screening and surveillance methods: correspondence **1183**
Banton C R, Thalayasingam B and Coulthard M G Spontaneous resolution of congenital nephrotic syndrome in a neonate **992**
Baraitser M *see* Holmström G *et al*
Barber J H *see* Usherwood T P *et al*
Barclay S M *see* Carter P E *et al*
Barlow J, Wilkinson M J and O'Callaghan C Neonatal cilia: ultrastructure **708** *fn*
Barnes N D *see* Noble-Jamieson G *et al*
Barrantes J *see* Muir K R *et al*
Barratt T M *see* Deal J E *et al*
  Gibb D M *et al*
Barros F C *see* Victora C G *et al*
Barton C *see* Newman C L *et al*
Bass D H, Wormald P J, McNally J and Rode H Topical anaesthesia for repair of minor lacerations **1272**
Batchelor L *see* Jones C *et al*
Baum J D *see* Stein A *et al*
Bax M C O and Whitmore K Health for all children: controversy—reviews of a book **141**
  see also Whitmore K and Bax M C O
Baxter P S *see* Taylor C J *et al*
Beardsmore C S *see* Caswell S J *et al*
  Thomson A H *et al*
Beardsmore S *see* Goldman A *et al*
Beasley M G *see* Smith I *et al*
Beasley S W *see* Freezer N J *et al*
  McLain B I *et al*
Becker M *see* Wagner N *et al*
Beetz R *see* Schofer O *et al*
Belhani M *see* de Montalembert M *et al*
Bentovim A *see* Sokel B S *et al*
Bergvall U *see* Mackenzie C A *et al*
Berry P J *see* James D *et al*
Berth-Jones J, Graham-Brown R A C and Burns D A Lichen sclerosus: correspondence reply **335**
Bertotto A, Castellucci G, Fabietti G, Scalise F and Vaccaro R Lymphocytes bearing the T cell receptor γδ in human breast milk **1274**
Bertrand P *see* Saliba E *et al*
Besley G T N *see* Cameron P D *et al*
Betts P R *see* Voss L D *et al*
  Walker J M *et al*
Bevan D H *see* Aylett S E *et al*
Bevis M and Taylor B What do school teachers know about asthma? **622**
Bhate S R *see* Clark A F *et al*
Bialek R *see* Wagner N *et al*
Bier D M, Fulginiti V A, Garfunkel J M, Lucey J F, Spranger J, Valman H B, Chiswick M L and Zetterstrom R Duplicate publication and related problems: editorial **1289**
Billington D *see* Dalzell A M *et al*
Bingham R M *see* Howard R F and Bingham R M
Bishop N J, King F J and Lucas A Linear growth in the early neonatal period **707** *fn*
  Ward P, Rennie J M and Dixon A K Paradoxical bone mineralisation in the twin to twin transfusion syndrome **705** *fn*
Bjure J *see* Krantz I *et al*
Black D, McFadyen A and Broster G Development of a psychiatric liaison service: personal practice **1373**
Blackwell P, Sikka S, Davies G N and Ravindranath C The school health service through parents' eyes: correspondence **336**
Blair M *see* MacMahon P *et al*
Blake K D, Russell-Eggitt I M, Morgan D W, Ratcliffe J M and Wyse R K H Who's in CHARGE? Multidisciplinary management of patients with CHARGE association **217**
Bleehen S S *see* Priestley B L and Bleehen S S
Blomstrand S Which routine test for kidney function: correspondence **561**
Bloomfield S and Farquhar J W Is a specialist paediatric diabetic clinic better? **139**
Bodden S J *see* Williams L H P and Bodden S J
Bohl J *see* Schofer O *et al*
Boland C and Thompson N L Effects of newborn screening of cystic fibrosis on reported maternal behaviour **1240**
Book Reviews
  Balistreri W F and Stocker J T, *editors*: Pediatric hepatology 1990. **1383**

Book Reviews
- Barness L A, de Vivo D C, Morrow G, Oski F and Rudolph A M, *editors*: Advances in pediatrics 1989. **815**
- Bax M, Hart H and Jenkins S M: Child development and child health 1990. **816**
- Becker K L *et al*, *editors*: Principles and practice of endocrinology and metabolism 1990. **1189**
- Behrman R E and Kliegman R, *editors*: Nelson's Essentials of pediatrics 1900. **1186**
- Berry C L, *editor*: Paediatric pathology, 2nd edition 1989. **1189**
- Black J: Child health in a multicultural society, 2nd edition 1989. **1187**
- Burg F D, Merril R E, Winter R J and Schaible D H, *editors*: Treatment of infants, children and adolescents 1990. **1188**
- Cassidy J T and Petty R E, *editors*: Textbook of pediatric rheumatology, 2nd edition 1990. **1382**
- Castells S and Finberg L, *editors*: Metabolic bone disease in children 1990. **1190**
- Chalmers D, Stewart I, Silva P and Mulvena A: Otitis media with effusion in children 1990. **1186**
- Children of Walsall: Health **341**
- Committee on clinical genetics working party report: Teaching genetics to medical students. A survey and recommendations 1990. **1189**
- Culbertson J, Krous H and Bendell R, *editors*: Sudden infant death syndrome 1988. **342**
- Davies K E, *editor*: The fragile X syndrome 1989. **342**
- De Vries L S, Dubowitz L M S, Dubowitz V and Pennock J M: A colour atlas of brain disorders in the newborn 1990. **814**
- Dinwiddie R: The diagnosis and management of paediatric respiratory disease 1990. **1381**
- Edmonds D K: Dewhurst's Practical paediatric and adolescent gynaecology, 2nd edition 1989. **339**
- Frank J D and Johnston J H, *editors*: Operative paediatric urology 1990. **1189**
- Garfinkel B D, Carlson G A and Weller E B, *editors*: Psychiatric disorders in children and adolescents 1990. **1187**
- Gill D and O'brien N: Paediatric clinical examination 1988. **340**
- Goodfellow P: Molecular medicine: cystic fibrosis 1989. **339**
- Graham J M, *reviser*: Smith's Recognizable patterns of human deformation 1988. **563**
- Hall D, *editor*: Health for all children 1989. **141**
- Halliday H L, McClure G and Reid M: Handbook of neonatal intensive care, 3rd edition 1989. **1187**
- Hamburger R N, *editor*: Food intolerance in infancy 1989. **562**
- Hann I M, Lake B D, Pritchard J and Lilleyman J, *editors*: Colour atlas of paediatric haematology 2nd edition 1990. **1383**
- Harvey D, Cooke R W I and Levitt G A, *editors*: The baby under 1000 g. 1989. **340**
- Hockaday J M, *editor*: Migraine in childhood 1988. **1188**
- Hogg C: NAWCH quality review – setting standards for children in health care 1989. **1383**
- Kingston H M: ABC of clinical genetics 1989. **338**
- Kolvin I, Miller F, Scott D, Gatzanis S and Fleeting M, *editors*: Continuities of deprivation? 1990. **1381**
- Lanzkowsky P, *editor*: Manual of pediatric hematology and oncology 1989. **563**
- Lask B and Fosson A: Childhood illness: the psychosomatic approach 1989. **814**
- Lister J and Irving I M, *editors*: Neonatal surgery, 3rd edition 1990. **1382**
- Logigian M K and Ward J D, *editors*: Pediatric rehabilitation 1989. **916**
- Long W A, *editor*: Fetal and neonatal cardiology 1990. **814**
- McDonald F, *compiler*: The parents' directory 1989. **342**
- McLaurin R, Venes J, Schut L and Epstein F, *editors*: Pediatric neurosurgery. Surgery of the developing nervous system. 2nd edition 1989. **344**
- McLean D M: Virological infections 1989. **343**
- Magalini S I, Magalini S C and de Francisci G, *editors*: Dictionary of medical syndromes 1990. **1191**
- Mason J K, *editor*: Paediatric forensic medicine and pathology 1989. **564**
- Mentzer W C and Wagner G M, *editors*: The hereditary hemolytic anemias 1989. **340**
- Moller J H and Neal W A: Fetal, neonatal, and infant cardiac disease 1990. **815**
- Morrisy R T, *editor*: Lovell and Winter's Pediatric orthopaedics, 3rd edition 1989. **1381**
- Nussbaum E, *editor*: Pediatric intensive care. 2nd edition 1989. **816**
- Ogden J A: Skeletal injury in the child 1990. **563**
- Orenstein D M: Cystic fibrosis: a guide for patient and family 1989. **563**
- Oski F A, DeAngelis C D, Feigin R D and Warshaw J B, *editors*: Principles and practice of pediatrics 1990. **1186**
- Pape K E and Wigglesworth J S, *editors*: Perinatal brain lesions 1989. **344**
- Phelan P D, Landau L I and Olinsky A: Respiratory illness in children, 3rd edition 1990. **1190**
- Polin R A and Ditmar M F, *editors*: Paediatric secrets 1989. **342**
- Raimondi A, Choux M and di Rocco C, *editors*: The pediatric spine III: cysts, tumours, and infections 1989. **562**
- Roberts K B, *editor*: Manual of clinical problems in pediatrics 1989. **916**
- Rowlands D J: Emergency cardiology 1989. **815**
- Royal College of Physicians - report: Prenatal diagnosis and genetic screening: community and service implications 1989. **916**
- Ruiz-Maldonado R, Parish L C and Beare J M, *editors*: Textbook of pediatric dermatology 1989. **338**
- Scherzer A L and Tscharnuter I: Early diagnosis and therapy in cerebral palsy 1990. **1187**
- Scriver C R and Childs B, *editors*: Garrod's Inborn factors in disease 1989. **343**
- Selikowitz M, *editor*: Down syndrome—the facts 1990. **1190**
- Shapiro D L and Notter R H, *editors*: Surfactant replacement therapy 1989. **341**
- Spufford M: Celebration 1989. **341**
- Stephenson J B P and King M D: Handbook of neurological investigations in children 1989. **339**
- Stockman O: Yearbook of pediatrics 1989. **339**
- Sutherland D H, Olshen R A, Biden E N and Wyatt M P, *editors*: The development of mature walking 1988. **1382**
- Tanner J M: Foetus into man 1989. **562**
- Tanner S: Paediatric hepatology 1989. **341**
- Thong Y H, *editor*: Textbook of paediatric practice 1989. **1188**
- Warne G L: Your child with congenital adrenal hyperplasia 1989. **1190**
- Waterlow J C, *editor*: Linear growth retardation in less developed countries. Nestle Nutrition Workshop Series, Vol 14 1988. **340**
- Weaver D D: Catalog of prenatally diagnosed conditions 1989. **343**
- Whitaker R H, *editor*: Current perspectives in paediatric urology 1989 **1191**
- Woo P, White P H and Ansell B M, *editors*: Paediatric rheumatology update 1990. **1383**

Booker P D *see* Hopkins C S *et al*

Booth I W *see* Brown G A and Booth I W
- Coombs R C *et al*
- Kolacek S *et al*
- Mayne A J *et al*
- Puntis J W L *et al*

Boralessa H *see* Lear G H *et al*

Borrell A *see* Fisk N M *et al*

Bos A P, Tibboel D, Hazebroek F W J, Stijnen T and Molenaar J C Congenital diaphragmatic hernia: impact of prostanoids in the perioperative period **994**

Bowmer C J *see* Miller P F W *et al*
- Ryan S W *et al*

Bowyer J J, Busst C M, Till J A, Lincoln C and Shinebourne E A Exercise ability after Mustard's operation **865**
and Sheppard M Capillary haemangioma presenting as a lung pseudocyst **1162**

Boyd R D H *see* Mohammed T *et al*

Boyd R H D Sister journals—the Soviet Union **1011**

Brackmann H H *see* Wagner N *et al*

Bradford R and Tomlinson L Psychological guidelines in the management of paediatric organ transplantation: personal practice **1000**

Brand J C *see* Miller J J *et al*

Branicki F J *see* Yeung C K *et al*

Branthwaite M A Long term outcome of ventilated asthmatics: commentary **1327**

Brett M M, Ghoneim A T M and Littlewood J M Serum IgA antibodies against *Pseudomonas aerugionosa* in cystic fibrosis **259**

Briend A, Hoque B A and Aziz K M A Iron in tubewell water and linear growth in rural Bangladesh **224**

British Paediatric Association future annual meetings, **1117**, **1226**, **1333**

British Paediatric Respiratory Group *see* Foundation for the study of infant deaths and the british paediatric respiratory group

Broadbent V *see* McLelland J *et al*

Brocklebank J T *see* Miller P F W *et al*
- Parkin A and Brocklebank J T
- Shaw N J *et al*

Brodehl J *see* Gordjani N *et al*
- Reusz G S *et al*

Brook C G D *see* Buyukgebiz A *et al*

Brooke O G *see* Lucas A *et al*
- Morley R *et al*

Broster G *see* Black D *et al*

Brown G A and Booth I W Clinical monitoring of steatorrhoea in cystic fibrosis: correspondence **913**
see also Kolacek S *et al*

Brown R A C Graham- *see* Graham-Brown R A C

Brownlie J *see* Hudson I R B *et al*

Buckle B G *see* Onadim Z O *et al*

Buick R G *see* Puntis J W L *et al*

Burge D M *see* Roberts J P and Burge D M
Burge P S *see* Freeman W *et al*
Burke J P *see* Huggon I C *et al*
Burns D A *see* Berth-Jones J *et al*
Burns S E *see* Hague R A *et al*
Busacca M *see* Cacciari E *et al*
Bush A, Busst C M, Knight W B, Hislop A A, Haworth S G and Shinebourne E A Changes in pulmonary circulation in severe bronchopulmonary dysplasia **739**
  see also Redington A and Bush A
Busst C M *see* Bowyer J J *et al*
  Bush A *et al*
Butt W *see* Ralston C and Butt W
Buyukgebiz A, Hindmarsh P C and Brook C G D Treatment of constitutional delay of growth and puberty with oxandrolone compared with growth hormone **448**

Cabezuelo-Huerta G *see* Frontera-Izquierdo P and Cabezuelo-Huerta G
Cacciari E, Zucchini S, Carla' G, Pirazzoli P, Cicognani A, Mandini M, Busacca M and Trevisan C Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance **1199**
Cameron P D, Dubowitz V, Besley G T N and Fensom A H Sialic acid storage disease **314**
Campbell C A *see* Smith G C *et al*
Capasso A *see* Greco L *et al*
Carla' G *see* Cacciari E *et al*
Carr R Marrow aspiration from small infants: correspondence **813**
Carswell F and Hamilton A Pathogenesis and management of aspergillosis in cystic fibrosis: correspondence **1288**
Carter P E, Barclay S M, Galloway W H and Cole G F Changes in bacterial meningitis **495**
Carter R *see* Kinmond S *et al*
Carter Y H *see* Bannon M J and Carter Y H
Cartwright K A V *see* Das B D *et al*
Carty H *see* Dalzell A M *et al*
Case C L, Oslizlok P, Fyfe D and Gillette P C Neonatal pneumomediastinum with isolated mitral obstruction **56** *fn*
Castellucci G *see* Bertotto A *et al*
Caswell S J, Thomson A H, Ashmore S P, Beardsmore C S and Simpson H Latent sensitisation to respiratory syncytial virus during acute bronchiolitis and lung function after recovery **946**
Catassi C, Natalini G, Rossini M, Rätsch I M, Coppa G V and Giorgi P L When should the coeliac patient have an intestinal biopsy?: correspondence **810**
Caul E O *see* Das B D *et al*
Cavanagh N P C *see* Chessells J M *et al*
Cayton R M *see* Freeman W *et al*
Chambers T L *see* Moss G D *et al*
Chang J *see* Irving W L *et al*
Chang M-H *see* Shieh C-C *et al*
Chapman B, O'Callaghan C, Coxon R, Glover P, Jaroszkiewicz G, Howseman A, Mansfield P, Small P, Milner A D and Coupland R E Estimation of lung volume in infants by echo planar imaging and total body plethysmography **168**
Chapman S and Hockey A D Aneurysms of the vein of Galen: correspondence **337**
Chaturvedi U C *see* Kumar R *et al*
Chen C-L *see* Shieh C-C *et al*
Cheng T O Contractural arachnodactyly versus Marfan's syndrome: correspondence **1012**
Chessells J M, Cox T C S, Kendall B, Cavanagh N P C, Jannoun L and Richards S Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation **416**
Chessells J M *see* Levitt G A *et al*
  Wheeler K and Chessells J M
Chiarelli F, la Penna G and Morgese G Early complications of diabetes mellitus: correspondence **247**
Chidiac P and Alexander I S Head retraction and respiratory disorders in infancy: annotation **567**
Chinn S *see* Gulliford M C *et al*
Chiswick M L Withdrawal of life support in babies: deceptive signals: personal view **1096** *fn*
Chiswick M L *see* Bier D M *et al*
  Gladman G and Chiswick M L
  Gladman G *et al*
  Sinha S K *et al*
Chita S K *see* Paladini D *et al*
Chow O K W *see* Fung K P *et al*
Cicognani A *see* Cacciari E *et al*
Claesson I *see* Krantz I *et al*
Clark A F, Tayler P J and Bhate S R Nocturnal faecal soiling and anal masturbation **1367**
Clark B J, Timms C and Franks W A Oculokinetic perimetry for the assessment of visual fields **432**
Clayden G S Examinations in paediatric training: medical education **1004**
Clayton P *see* Ichimiya H *et al*
Colditz P R *see* Moorthy B *et al*
Cole C B *see* Hall M A *et al*
Cole G F *see* Carter P E *et al*
Cole T J *see* Lucas A *et al*
  Morley C J *et al*
  Morley R *et al*
  Thornton A J *et al*
Cole W G *see* Kiers L *et al*
Coleman E D *see* Shaw R A *et al*
Collins J E, Leonard J V, Teale D, Marks V, Williams D M, Kennedy C R and Hall M A Hyperinsulinaemic hypoglycaemia in small for dates babies **1118**
Collins M A *see* Pasi K J *et al*
Colver A Health for all children: controversy—reviews of a book **142**
  see also Jarvis S N *et al*
Congdon P J, Horsman A, Ryan S W, Truscott J G and Durward H Spontaneous resolution of bone mineral depletion in preterm infants **1038** *fn*
Conway E *see* Priftis K *et al*
Conway S P, Phillips R R and Panday S Admission to hospital with gastroenteritis **579**
  see also Simmonds E J *et al*
Cooke A *see* Hudson I *et al*
Cooke R W I Cerebral palsy in very low birthweight infants **201**
  see also Marlow N *et al*
  Pharoah P O D *et al*
Cooke T *see* Pharoah P O D *et al*
Coombs R C, Morgan M E I, Durbin G M, Booth I W and Mcneish A S Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin **1067** *fn*
Coppa G V *see* Catassi C *et al*
Corrah T *see* Sullivan P B *et al*
Coulthard M *see* Lambert H *et al*
Coulthard M G *see* Banton C R *et al*
  Skinner R *et al*
  Wilson D I *et al*
Coupland R E *see* Chapman B *et al*
Court S *see* Dale A and Court S
Cowell J K *see* Onadim Z O *et al*
Cox T C S *see* Chessells J M *et al*
Coxon R *see* Chapman B *et al*
Craft A W *see* Morris-Jones P H and Craft A W
  Skinner R *et al*
Crane J *see* Shaw R A *et al*
Cross J H, Eminson J and Wharton B A Ramadan and birth weight at full term in Asian Moslem pregnant women in Birmingham **1053** *fn*
Crouchman M Head injury—how community paediatricians can help: personal practice **1286**
Crowne E C, Shalet S M, Wallace W H B, Eminson D M and Price D A Final height in boys with untreated constitutional delay in growth and puberty **1109**
Cudmore R E *see* Walker J and Cudmore R E
Cumming K *see* Voss L D *et al*
Cummins C *see* Kyle D *et al*
Cunningham A L *see* Irving W L *et al*
Curtis M de *see* de Curtis M

Da Dalt L, Mazzoleni S, Montini G, Donzelli F and Zachello F Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux: correspondence reply **560**
Da Mota H C The taste of milk: correspondence **647**
Dab I *see* Toppet M *et al*
Dale A and Court S *Haemophilus influenzae* infections in siblings: the need for prophylaxis **489**
Dale P A *see* Drake D P and Dale P A
Dalt L da *see* da Dalt L
Dalton R N *see* Roberts D S *et al*
Dalzell A M and Heaf D P Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis **788**
  and Carty H Pathology mimicking distal intestinal obstruction syndrome in cystic fibrosis **540**
  van Saene H K F and Heaf D P Cystic fibrosis, *Pseudomonas aeruginosa*, and selective decontamination **1365**
  Freestone N S, Billington D and Heaf D P Small intestinal permeability and orocaecal transit time in cystic fibrosis **585**
Daman-Willems C *see* Kennedy J D *et al*
Darby C R *see* Wilson J M and Darby C R
Darbyshire P J *see* Sartori P C E *et al*
Das B D, Lakhani P, Kurtz J B, Hunter N, Watson B E, Cartwright K A V, Caul E O and Roome A P C H Congenital rubella after previous maternal immunity **545**
Das V K Prevalence of otitis media with effusion in children with bilateral sensorineural hearing loss **757**
David T J Cystic fibrosis: personal practice **152**

Davidson D C and Watling R M Glucose polymer regimens and hypernatraemia: correspondence **1185**
Davidson P M *see* Mclain B I *et al*
Davies D P Growth hormone deficiency in children with chromosomal abnormalities: correspondence **1183**
  and Leung S S F Surveillance for anaemia: risk factors in pattern of milk intake: correspondence **1184**
Davies E T *see* Hadžić N *et al*
Davies G N *see* Blackwell P *et al*
Davies H, Gordon I, Matthew D J, Helms P, Kenney I J, Lutkin J E and Lenney W Long term follow up after inhalation of foreign bodies **619**
Davies P A, Milner A D, Silverman M and Simpson H Monitoring and sudden infant death syndrome: correspondence **913**
Davis D P *see* Fung K P *et al*
De Curtis M, Senterre J and Rigo J Renal solute load in preterm infants **357** *fn*
De Fusco C *see* Greco L *et al*
De Jonge G A *see* Engelberts A C and De Jonge G A
De Montalembert M, Girot R, Revillon Y, Jan D, Adjrad L, Ardjoun F Z, Belhani M and Najean Y Partial splenectomy in homozygous beta thalassaemia **304**
De Santi M M, Magni A, Valletta E A, Gardi C and Lungarella G *Hydrocephalus*, bronchiectasis, and ciliary aplasia **543**
De Silva P, Earl U and Sinha S Complication of a central venous line in the newborn: correspondence **915**
Deal J E, Sever P S, Barratt T M and Dillon M J Phaeochromocytoma—investigation and management of 10 cases **269**
  Shah V, Goodenough G and Dillon M J Red cell membrane sodium transport: possible genetic role and use in identifying patients at risk of essential hypertension **1154**
Dear P R F *see* Ng P C *et al*
  Shaw N J and Dear P R F
Der Meer S B van *see* van der Meer S B
Der Voort E van *see* van der Voort E
Derbyshire G *see* Seshia S S *et al*
Derde M P *see* Toppet M *et al*
Devane S P *see* Sokel B S *et al*
Devlin J B and O'Cathain C Predicting treatment outcome in nocturnal enuresis **1158**
Di Gregorio F *see* Leonardi S *et al*
Di Palma A *see* Politis C *et al*
Dillon M J *see* Deal J E *et al*
  Gibbs J *et al*
  Kennedy J D *et al*
  Lask B and Dillon M J
  Suzuki A *et al*
Dinwiddie R *see* Kennedy J D *et al*
Dixon A K *see* Bishop N J *et al*
Dobson S R M *see* Webber S *et al*
Donzelli F *see* da Dalt L *et al*
Dooley S L *see* Metzger B E *et al*
Dos Anjos R *see* Murdoch I A and Dos Anjos R
Doyle L W *see* Sennhauser F H *et al*
Drake D P and Dale P A Topical anaesthesia for repair of minor lacerations: commentary **1274**
Drumm B *Helicobacter pylori:* regular review **1278**
D'Souza S W *see* Sinha S K *et al*
  see also Wallace G *et al*
Dubowitz V *see* Cameron P D *et al*
Duck S C *see* Schwarz H P and Duck S C
Duerden B I *see* Taylor C J *et al*
Dunbar E M *see* Fox R *et al*
Dunger D *see* Gibb D M *et al*
Dunger D B *see* Ahmed M L *et al*
  Gibb D M *et al*
Dunn P M Charles-Michel Billard (1800–1832): pioneer of neonatal medicine: perinatal lessons from the past **711** *fn*
  Charles White (1728–1813) and natural birth: perinatal lessons from the past **395** *fn*
  Dr von Reuss on continuous positive airway pressure in 1914: perinatal lessons from the past **68** *fn*
  Dr William Harvey (1578–1657): physician, obstetrician, and fetal physiologist: perinatal lessons from the past **1098** *fn*
  Is late walking a marker of congenital displacement of the hip?: correspondence **1183**
  Life saving intervention in the neonatal period: dilemmas and decisions **557**
Dunstan R *see* Irving W L *et al*
Durbin G M *see* Coombs R C *et al*
Durward H *see* Congdon P J *et al*

Earl U *see* de Silva P *et al*
Earley A, Valman H B, Altman D G and Pippard M J Microcytosis, iron deficiency, and thalassaemia in preschool children **610**
Eastham E J *see* Murphy M S *et al*
  Sullivan P B *et al*
Edwards A G K, Halse P C, Parkin J M and Waterston A J R Recognising failure to thrive in early childhood **1263**
Eeckels R *see* Roy S K *et al*
Egger M, Mäusezahl D, Odermatt P, Marti H-P and Tanner M Symptoms and transmission of intestinal cryptosporidiosis **445**
Eggitt I M Russell- *see* Russell-Eggitt I M
Ehrich J H H *see* Reusz G S *et al*
El-Radhi A S Effect of fever on recurrence rate of febrile convulsions: correspondence reply **334**
Elias-Jones A C, Jaspan T, Mellor D H and Worthington B S Magnetic resonance imaging in neurological disorders **922**
Ellis A M *see* Marlow N *et al*
Ellis J *see* Ahmed F *et al*
Ellis M E *see* Fox R *et al*
Emery J L, Scholey S and Taylor E M Decline in breast feeding **369** *fn*
  see also Taylor E M and Emery J L
Eminson D M *see* Crowne E C *et al*
Eminson J *see* Cross J H *et al*
Engleberts A C and de Jonge G A Choice of sleeping position for infants: possible association with cot death: current topic **462**
Eriksson B *see* Krantz I *et al*
Evans A J *see* Walker J M *et al*
Evans D H *see* Fenton A C *et al*
Evans E G V *see* Simmonds E J *et al*
Evans N *see* Agnarsson U *et al*
Evans N J and Archer L N J Postnatal circulatory adaptation in healthy term and preterm neonates **24** *fn*
Evans N Lloyd *see* Lloyd-Evans N
Evans P M, Evans S J W and Alberman E Cerebral palsy: why we must plan for survival **1329**
Evans S J W *see* Evans P M *et al*
Everard M and Milner A D Pressure flow characteristics of the valve in spacer devices: correspondence **159**
Ewer A K *see* Pasi K J *et al*

Fabietti G *see* Bertotto A *et al*
Fagan D G *see* Wilkinson M J and Fagan D G
Farmer G *see* Stewart G and Farmer G
Farquhar J W *see* Bloomfield S and Farquhar J W
Farrell K *see* Appleton R E *et al*
Feng C S *see* Fok T F *et al*
Fensom A H *see* Cameron P D *et al*
Fenton A C, Evans D H and Levene M I On line cerebral blood flow velocity and blood pressure measurement in neonates: a new method **11** *fn*
  Field D J, Woods K L, Evans D H and Levene M I Circulatory effects of fast ventilator rates in preterm infants **662** *fn*
Ferson M J Immunisation state and its documentation in hospital patients **763**
Festen C *see* Reijnen J A M *et al*
Field D J *see* Fenton A C *et al*
Field N J G *see* Freeman W *et al*
Fielder A R *see* Robinson J and Fielder A R
  Robinson J *et al*
Fields J *see* Williams J *et al*
Finn A, Hadžić N, Morgan G, Strobel S and Levinsky R J Prognosis of chronic granulomatous disease **942**
Fireman P *see* Skoner D P and Fireman P
Firmin R *see* Thomson A H *et al*
Fisfis M *see* Politis C *et al*
Fisk N M, Borrell A, Hubinont C, Tannirandorn Y, Nicolini U and Rodeck C H Fetofetal transfusion syndrome: do the neonatal criteria apply in utero? **657** *fn*
Fleming P *see* James D *et al*
Fletcher H J, Ibrahim S A and Speight N Survey of asthma deaths in the Northern region, 1970–85 **163**
Floyd C A *see* Freeman W *et al*
Fok T F, So L Y, Leung K W, Wong W, Feng C S and Tsang S S Use of peripheral vessels for exchange transfusion **676** *fn*
  see also Sung R Y T *et al*
Foley H Treatment of epilepsy in people with multiple handicap: personal practice **453**
Foot A B M, Oakhill A and Mott M G Cryptosporidiosis and acute leukaemia **236**
  see also Gibb D M *et al*
Foote K D, Hoon A H, Sheps S, Gunawardene N R, Hershler R and Pendray M R Peak inspiratory pressure requirements in infants born weighing less than 750 g **1045** *fn*
Ford R P K *see* Williams S M *et al*
Forget P P *see* van der Meet S B *et al*
Forrest G C *see* Stein A *et al*
Forster G E *see* Powell K *et al*
Forsyth J S *see* Phillips G *et al*
Forsythe I *see* Ryan S W *et al*
Foundation for the study of infant deaths and the british paediatric respiratory group Monitoring and sudden infant death syndrome: an update: current topic **238**: correspondence **913**

Fowler M A *see* Morley C J *et al*
  Thornton A J *et al*
Fox R, Leen C L S, Dunbar E M, Ellis M E and Mandal B K Acute gastroenteritis in infants under 6 months old **936**
Franks R and Rothera M Cardiopulmonary bypass for resection of low tracheal haemangioma **630**
Franks W A *see* Clark B J *et al*
Freeman J M *see* Shuper A *et al*
Freeman W, Weir D C, Whitehead J E, Rogers D I, Sapiano S B, Floyd C A, Kirk P M, Stalker C R, Field N J G, Cayton R M and Burge P S Association between risk factors for coronary heart disease in schoolboys and adult mortality rates in the same localities **78**
Freestone N S *see* Dalzell A M *et al*
Freezer N J, Beasley S W and Robertson C F Tracheostomy **123**
Freinkel N *see* Metzger B E *et al*
Frontera-Izquierdo P and Cabezuelo-Huerta G Natural and modified history of complete atrioventricular septal defect—a 17 year study **964**
Fu K H *see* Yeung C K *et al*
Fuglsang G *see* Pedersen S *et al*
Fulginiti V A *see* Bier D M *et al*
Fuller R *see* Hall M A *et al*
Fung K P, Lau S P, Chow O K W, Lee J and Wong T W Effects of overweight on lung function **512**
  Lee J, Lau S P, Chow O K W, Wong T W and Davis D P Properties and clinical implications of body mass indices **516**
Fusco C de *see* de Fusco F
Fyfe D *see* Case C L *et al*

Gagliardi L Qualitative expressions of probability: is there any real misunderstanding: correspondence **1379**
Galasko C S B *see* Williamson J B *et al*
Galea P and Goel K M Visceral leishmaniasis in a Scottish child **1269**
  Salicylate poisoning in dermatological treatment: correspondence **335**
  see also Macdonald P D *et al*
Galloway W H *see* Carter P E *et al*
Gandy G and Rennie J Antibiotic treatment of suspected neonatal meningitis: annotation **1** *fn*: correspondence reply **810**
Gardi C *see* de Santi M M *et al*
Gardiner R M The human genome: a prospect for paediatrics: regular review **457**
Garfunkel J M *see* Bier D M *et al*
George R H *see* Mayne A J *et al*
Ghoneim A T M *see* Brett M M *et al*
  Simonds E J *et al*
Gianantonio C A *see* Perelstein E M *et al*
Giasanti A *see* Politis C *et al*
Gibb D and Levin M Intravenous immunoglobulin in HIV infection: correspondence **247**
Gibb D M, Dunger D, Levin M, Grant D, Jones P and Barratt T M Absence of effect of dipyridamole on renal and platelet function in diabetes mellitus **93**
  Foot A B M, May B, Parish H, Strang S, Grant D B and Dunger D B Human isophane or lente insulin? A double blind crossover trial in insulin dependent diabetes mellitus **1334**
Gibbs J, Dillon M J, Lang S, Meghji S and Pritchard J Indomethacin responsive hypercalcaemia associated with a renal sarcoma **1168**
Gibson B E S *see* Hudson I R B *et al*
Gilbert J *see* Walters M P *et al*
Gilbertson N J, Taylor J W and Kovar I Z Mosaic trisomy 16 in a live newborn infant **388** *fn*
Gillette P C *see* Case C L *et al*
Gilmore D H *see* Swinhoe D J *et al*
Gimenez M I *see* Perelstein E M *et al*
Giorgi P L *see* Catassi C *et al*
Girot R *see* de Montalembert M *et al*
Gladman G and Chiswick M L Skin conductance and arousal in the newborn **1063** *fn*
  Sinha S, Sims D G and Chiswick M L *Staphylococcus epidermidis* and retention of neonatal percutaneous central venous catheters **234**
Glasgow J F T *see* Porter J D H *et al*
Glickman M *see* Hall S M and Glickman M
Glover P *see* Chapman B *et al*
Gluckman P D *see* Walker K *et al*
Goddard O *see* Johnson A *et al*
Godwin P G R *see* Hoy C *et al*
Goel K M *see* Galea P and Goel K M
Gold F *see* Saliba E *et al*
Goldman A, Beardsmore S and Hunt J Palliative care for children with cancer—home, hospital, or hospice?: personal practice **641**
Gooch V *see* Suzuki A *et al*
Goodenough G *see* Deal J E *et al*
Goodyear H M and Harper J I Atopic eczema, hyponatraemia, and hypoalbuminaemia **231**
Gordjani N, Offner G, Hoyer P F and Brodehl J Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine **275**
Gordon G J *see* Sartori P C E *et al*
Gordon I *see* Davies H *et al*
Gordon N Health for all children: correspondence **812**
  see also Jones C *et al*
Goulder P, Seward D and Hatton C Intravenous immunoglobulin in virus associated haemophagocytic syndrome **1275**
Graham P J Maternal employment: annotation **565**
Graham-Brown R A C *see* Berth-Jones J *et al*
Grannum P A T *see* Moya F R *et al*
Grant D *see* Gibb D M *et al*
Grant D B *see* Gibb D M *et al*
  Ng W K *et al*
Grattan-Smith P *see* Irving W L *et al*
Greco L, Capasso A, de Fusco C and Paludetto R Pulsatile weight increases in very low birthweight babies appropriate for gestational age **373** *fn*
Green A *see* Houtman P N *et al*
Green A Aynsley- *see* Aynsley-Green A
Green O C *see* Metzger B E *et al*
Green S H *see* Roberts-Harry J *et al*
Greene S A Early complications of diabetes mellitus: correspondence **247**
Greenough A Bronchopulmonary dysplasia: early diagnosis, prophylaxis, and treatment: personal practice **1082** *fn*
  see also Thompson P J *et al*
  Yuksel B *et al*
Greenwood B M *see* Sullivan P B *et al*
Gregorio F di *see* di Gregorio F
Groot-Loonen J J, Pinkerton C R, Morris-Jones P H and Pritchard J How curable is relapsed Wilms' tumour? **968**
Gross R J *see* Kleanthous H *et al*
Grunfeld B G *see* Perelstein E M *et al*
Gulliford M C, Price C E, Rona R J and Chinn S Sleep habits and height at ages 5 to 11 **119**
Gunasekaran T *see* Ichimiya H *et al*
Gunawardene N R *see* Foote K D *et al*
Gunn A J *see* Walker K *et al*
Gustafsson P M, Kjellman N-I M, and Tibbling L Bronchial asthma and acid reflux into the distal and proximal oesophagus **1255**
Guttridge B *see* Milford D V *et al*

Hackeng W H L *see* van Steensel-Moll H A *et al*
Hadžić N, Portmann B, Davies E T, Mowat A P, and Mieli-Vergani G Acute liver failure induced by carbamazepine **315**
  see also Finn A *et al*
Haggard M P Hearing screening in children—state of the art(s): annotation **1193**
Hague R A, Burns S E, Mok J Y Q and Yap P L Diagnosis of *Pneumocystis carinii* pneumonia from non-invasive sampling of respiratory secretions **1364**
Haider R *see* Roy S K *et al*
Hall D Health for all children: controversy—reviews of a book **141**
Hall D M B Health for all children: correspondence **812**
  Johnson S L J and Middleton J Rehabilitation of head injured children: personal practice **553**
Hall J G Genomic imprinting: annotation **1013** *fn*
Hall M A, Cole C B, Smith S L, Fuller R and Rolles C J Factors influencing the presence of faecal lactobacilli in early infancy **185**
  see also Collins J E *et al*
Hall S K *see* Houtman P N *et al*
Hall S M and Glickman M Report from the British Paediatric Surveillance Unit: British Paediatric Association **807**
  see also Milford D V *et al*
  Porter J D H *et al*
Halliday H L and McClure G Arteriovenous malformations in the vein of Galen: correspondence **559**
Hällström O *see* Mäki M *et al*
Halse P. *see* Jarvis S N *et al*
Halse P C *see* Edwards A G K *et al*
Hamilton A *see* Carswell F and Hamilton A
Hampton F J, MacFadyen U M and Simpson H Reproducibility of 24 hour oesophageal pH studies in infants **1249**
Handy D J *see* Mayne A J *et al*
Hansen O R *see* Pedersen S *et al*
Harper I A *see* Phillips G *et al*
Harper J I *see* Goodyear H M and Harper J I
Harper K *see* Onadim Z O *et al*
Harrington C I Lichen sclerosus: correspondence **335**
Harry J *see* Muir K R *et al*
Harry J Roberts- *see* Roberts-Harry J
Hartley R *see* Ryan S W *et al*
Haslam J S *see* Asthana J C *et al*
Hathaway M *see* James D *et al*
Hatton C *see* Goulder P *et al*
Hawkins M M, Kingston J E and Wilson L M K Late deaths after treatment for childhood cancer **1356**
Haworth J C *see* Seshia S S *et al*

Haworth M *see* Ryan S W *et al*
Haworth S G *see* Bush A *et al*
  Suzuki A *et al*
Haycock G B *see* Roberts D S *et al*
Hayward R Craniosynostosis and the paediatrician: annotation **568**
Hazebroek F W J *see* Bos A P *et al*
Hazelzet J A *see* van Steensel-Moll H A *et al*
Heaf D P *see* Dalzell A M and Heaf D P
  Dalzell A M *et al*
  Seddon P C and Heaf D F
Heaton P Crytosporidiosis and acute leukaemia: correspondence **813**
Heird W C *see* Isaacs C E *et al*
Helms P *see* Davies H *et al*
  Russell R I R and Helms P J
Henry R L Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux: correspondence **560**
Herbert E D *see* Price D A *et al*
Hershler R *see* Foote K D *et al*
Hewson P H, Humphries S M, Roberton D M, Mcnamara J M and Robinson M J Markers of serious illness in infants under 6 months old presenting to a children's hospital **750**
  see also Morley C J *et al*
  Thornton A J *et al*
Hey E N *see* Appleton R E *et al*
Heykants J *see* Marlow N *et al*
Hill F G H *see* Pasi K J *et al*
Hill S M and Milla P J Colitis caused by food allergy in infants **132**
Hiller E J Pathogenesis and management of aspergillosis in cystic fibrosis: annotation **397**; correspondence reply **1288**
  see also Rayner R J *et al*
Himes J H and Roche A F Parent-specific evaluation of growth: correspondence **647**
Hindmarsh P C *see* Buyukgebiz A *et al*
Hislop A A *see* Bush A *et al*
Hobbs C J and Wynne J M The sexually abused battered child **423**
Hockaday J M Management of migraine: personal practice **1174**
Hockey A D *see* Chapman S and Hockey A D
Hodges S, O'Malley B P, Northover B N, Woods K L and Swift P G F Reappraisal of thyroxine treatment in primary hypothyroidism **1129**
Hoff W G van't *see* van't Hoff W G
Holden C E *see* Puntis J W L *et al*
Holland B *see* Hudson I *et al*
Holland B M *see* Hudson I R B *et al*
Holm K *see* Mäki M *et al*
Holmes S J K *see* Aylett S E *et al*
Holmström G, Almond G, Temple K, Taylor D and Baraitser M The iris in Williams syndrome **987**
Honour J W *see* Midgley P C *et al*
  Priftis K *et al*
Hoogstraten J *see* Seshia S S *et al*
Hoon A H *see* Foote K D *et al*
Hope P L *see* Moorthy B *et al*
  Webber S *et al*
Hopkins C S, Underhill S and Booker P D Pharmacokinetics of paracetamol after cardiac surgery **971**
Hoque B A *see* Briend A *et al*
Horsman A *see* Congdon P J *et al*
Houston A *see* Hudson I *et al*
Houston A B *see* White M P and Houston A B
Houston I B *see* Jewkes F E M *et al*
  Lewis M A *et al*
Houtman P N, Hall S K, Green A and Rylance G W Rapid anticonvulsant monitoring in an epilepsy clinic **264**
Howard E R *see* Page A C *et al*
Howard R F and Bingham R M Endotracheal compared with intravenous administration of atropine **449**
Howden R *see* Taylor C J *et al*
Howseman A *see* Chapman B *et al*
Hoy C, Millar M R, Mackay P, Godwin P G R, Langdale V and Levene M I Quantitative changes in faecal microflora preceding necrotising enterocolitis in premature neonates **1057** *fn*
Hoyer P F *see* Gordjani N *et al*
  Reusz G S *et al*
Hubinont C *see* Fisk N M *et al*
Huddart S N *see* Muir K R *et al*
Hudson I, Cooke A, Holland B, Houston A, Jones J G, Turner T and Wardrop C A J Red cell volume and cardiac output in anaemic preterm infants **672** *fn*
  Houston A, Aitchison T, Holland B and Turner T Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound **15** *fn*
Hudson I R B, Gibson B E S, Brownlie J, Holland B M, Turner T L and Webber R G Increased concentrations of D-dimers in newborn infants **383** *fn*
Huerta G Cabezuelo- *see* Cabezuelo-Huerta G
Huggon I C, Burke J P and Talbot J F Contractural arachnodactyly with mitral regurgitation and iridodonesis **317**
Hughes I A Monitoring treatment in congenital adrenal hyperplasia: correspondence **333**
  see also Ng W K *et al*
Hughes I A *see* Young M C and Hughes I A
Hughes-Davies T H Patients who do not come: correspondence **913**
Humphries S M *see* Hewson P H *et al*
Hungerford J L *see* Onadim Z O *et al*
Hunt J *see* Goldman A *et al*
Hunter D *see* John R M *et al*
Hunter E W *see* Scott J E S *et al*
Hunter N *see* Das B D *et al*
Huttly S R A *see* Victora C G *et al*

Ibrahim S A *see* Fletcher H J *et al*
Ichimiya H, Nazer H, Gunasekaran T, Clayton P and Sjövall J Treatment of chronic liver disease caused by 3β-hydroxy-$\Delta 5$-C_{27}-steroid dehydrogenase deficiency with chenodeoxycholic acid **1121**
Illingworth R S Book reviews, some personal experience from the receiving end: spring books **338**
Irving W L, Chang J, Raymond D R, Dunstan R, Grattan-Smith P and Cunningham A L Roseola infantum and other syndromes associated with acute HHV6 infection **1297**
Isaacs C E, Kashyap S, Heird W C and Thormar H Antiviral and antibacterial lipids in human milk and infant formula feeds **861**
Isaacs D Cold comfort for the catarrhal child: annotation **1295**
  see also Webber S *et al*
Ispahani P *see* Rayner R J *et al*
Ito S *see* Ueda N *et al*
Ives K N *see* Moorthy B *et al*
Izquierdo P Frontera- *see* Frontera-Izquierdo P

Jackson A A *see* Ahmed F *et al*
Jackson A D M Acrodynia ('pink disease'): forty years ago **1182**
  Caffey's syndrome: forty years ago **1164**
  Coeliac disease: forty years ago **609**
  Childhood morbidity 1947–9: forty years ago **1182**
  Congenital hypoplastic anaemia: forty years ago **1363**
  Gastroenteritis: forty years ago **526**
  Giardia lamblia infestation: forty years ago **767**
  Haemolytic disease of the newborn: forty years ago **1363**
  Infantile cortical hyperostosis: forty years ago **1164**
  Pulmonary collapse in pertussis: forty years ago **526**
  Studies in neonates: forty years ago **767**
  Thrush in infancy: forty years ago **1164**
  Tonsillectomy: forty years ago **767**
Jackson S K, Parton J, Shortland G, Stark J M and Thompson E N Serum immunoglobulins to endotoxin core glycolipid: establishment of normal concentrations **768**: correspondence reply **1379**
  Serum immunoglobulins to endotoxin core glycolipid: acute leukaemia and other cancers **771**
Jaeken J *see* Stibler H and Jaeken J
James D Diagnosis and management of fetal growth retardation: current topic **390** *fn*
  Berry P J, Fleming P and Hathaway M Surfactant abnormality and the sudden infant death syndrome—a primary or secondary phenomenon? **774**
  see also Pillai M and James D
Jamieson G Noble- *see* Noble-Jamieson G
Jan D *see* de Montalembert M *et al*
Jannoun L *see* Chessells J M *et al*
Jaroszkiewicz G *see* Chapman B *et al*
Jarvis S N, Waterston A, Halse P, Paynter A, Jones P and Colver A The extended role of the new school doctor: correspondence **559**
Jarvis S N *see* Tamhne R C *et al*
Jaspan T *see* Elias-Jones A C *et al*
Jay M *see* Onadim Z O *et al*
Jenkins H R and Ansari B M Management of gastroenteritis **939**
Jewkes F E M, Mcmaster D J, Napier W A, Houston I B and Postlethwaite R J Home collection of urine specimens—boric acid bottles or Dipslides? **286**
John R M, Hunter D and Swanton R H Echocardiographic abnormalities in type IV mucopolysaccharidosis **746**
Johnson A and Ashurst H Screening for sensorineural deafness by health visitors **841**
Johnson A, Goddard O and Ashurst H Is late walking a marker of morbidity? **486**: correspondence reply **1184**
Johnson S L J *see* Hall D M B *et al*
Jones A C Elias- *see* Elias-Jones A C
Jones C, Batchelor L, Gordon N and West M The five year school medical—time for a change: correspondence **912**
Jones J Berth- *see* Berth-Jones J
Jones J G *see* Hudson I *et al*
Jones K *see* Moss A L H *et al*

Jones K V Antimicrobial treatment for urinary tract infections: current topic **327**
Jones P *see* Gibb D M *et al*
Jarvis S N *et al*
Jones P H Morris- *see* Morris-Jones P H
Jonge G A de *see* de Jonge G A

Karani J *see* Page A C *et al*
Kashyap S *see* Isaacs C E *et al*
Kastrup K W *see* Main K *et al*
Katerelos C *see* Messaritakis J *et al*
Kaur B and Taylor D Retinal haemorrhages: current topic **1369**
Kelleher J *see* Walters M P *et al*
Kendall B *see* Chessells J M *et al*
Kennedy C R *see* Collins J E *et al*
Kennedy J D, Dinwiddie R, Daman-Willems C, Dillon M J and Matthew D J Pseudo-Bartter's syndrome in cystic fibrosis **786**
Kenney I J *see* Davies H *et al*
Kent A, Murphy G H and Milla P Psychological characteristics of children with Shwachman syndrome **1349**
Khatun M *see* Roy S K *et al*
Kiely E M Surgery for gastro-oesophageal reflux: annotation **1291**
see also Malone P S and Kiely E M
Kiers L, Shield L K and Cole W G Neurological manifestations of osteoid osteoma **851**
King F J *see* Bishop N J *et al*
Kingston H M *see* Asthana J C *et al*
Kingston J E *see* Hawkins M M *et al*
Kinmond S, Carter R, Skeoch C H and Morton N S Nephroblastoma presenting with acute hepatic encephalopathy **542**
Kinnon C and Levinsky R J Somatic gene therapy for genetic disease: annotation **72**
Kirk J M W *see* Richardson R J and Kirk J M W
Kirk P M *see* Freeman W *et al*
Kjellman N-I M *see* Gustafsson P M *et al*
Kleanthous H, Smith H R, Scotland S M, Gross R J, Rowe B, Taylor C M and Milford D V Haemolytic uraemic syndromes in the British Isles, 1985–8: association with Verocytotoxin producing *Escherichia coli*. Part 2: microbiological aspects **722**
see also Milford D V *et al*
Knight W B *see* Bush A *et al*
Knights B and Pandey S K Paradoxical approach to the management of faecal incontinence in normal children **598**
Kolacek S, Puntis J W L, Lloyd D R, Brown G A and Booth I W Ontogeny of pancreatic exocrine function **178**
Koskimies S *see* Mäki M *et al*
Kovar I Z *see* Gilbertson N J *et al*
Macmahon P *et al*
Krantz I, Bjure J, Claesson I, Eriksson B, Sixt R and Trollfors B Respiratory sequelae and lung function after whooping cough in infancy **569**
Krohn H P *see* Reusz G S *et al*
Kruse K *see* Schofer O *et al*
Kumar A *see* Kumar R *et al*
Kumar R, Mathur A, Kumar A, Sethi G D, Sharma S and Chaturvedi U C Virological investigations of acute encephalopathy in India **1227**
Kuno K *see* Ueda N *et al*
Kurlemann G and Palm D G Growth failure secondary to moyamoya syndrome: correspondence **1012**
Kurtz J B *see* Das B D *et al*
Kyle D, Sunderland R, Stonehouse M, Cummins C and Ross O Ethnic differences in incidence of sudden infant death syndrome in Birmingham **830**

La Penna G *see* Chiarelli F *et al*
Lakhani P *see* Das B D *et al*
Lam B C C, Wong H N and Yeung C Y Effect of indomethacin on binding of bilirubin to albumin **690** *fn*
Lambert H, Morris K, Sharp J and Coulthard M Access for peritoneal dialysis in neonates and infants: correspondence **914**
Lang S *see* Gibbs J *et al*
Langdale V *see* Hoy C *et al*
Laoide S *see* Watkin P M *et al*
Lask B and Dillon M J Postviral fatigue syndrome: annotation **1198**
Laskari H *see* Messaritakis J *et al*
Lau J *see* Sung R Y T *et al*
Lau S P *see* Fung K P *et al*
Laugier J *see* Saliba E *et al*
Lazaro C San *see* san Lazaro C
Leach F N Management of threadworm infestation during pregnancy: annotation **399**
Leanage R *see* Thomson A H *et al*
Lear G H, Mckenzie S A and Boralessa H Management of acute upper airway obstruction in an intensive care unit in a district general hospital: personal practice **241**
Lee A *see* Spencer J A D *et al*
Lee J *see* Fung K P *et al*
Lee R E J *see* Appleton R E *et al*
Scott J E S *et al*
Wilson D I *et al*
Leen C L S *see* Fox R *et al*
Leggio T *see* Leonardi S *et al*
Lenney W *see* Davies H *et al*
Leonard J V *see* Collins J E *et al*
Leonardi S, Leggio T, Sciacca' A, di Gregorio F and Musumeci S Intradermal hepatitis B vaccination in thalassaemia **527**
Leung K W *see* Fok T F *et al*
Leung S S F *see* Davies D P and Leung S S F
Levene M I Cerebral ultrasound and neurological impairment: telling the future: annotation **469**
see also Fenton A C *et al*
Hoy C *et al*
Levene S and Mckenzie S A Transcutaneous oxygen saturation in sleeping infants: prone and supine **524**
Levin M *see* Gibb D and Levin M
Levin M *see* Gibb D M *et al*
Levinsky R J *see* Finn A *et al*
Kinnon C and Levinsky R J
Levitt G A, Stiller C A and Chessells J M Prognosis of Down's syndrome with acute leukaemia **212**
Lewis M A, Houston I B and Postlethwaite R J Access for peritoneal dialysis in neonates and infants **44** *fn*
Lewis S Paediatrician to a special school: personal practice **803**
Liddle B J Herpes simplex infections in atopic eczema: correspondence **333**
Lincoln C *see* Bowyer J J *et al*
Lindsell D *see* Webber S *et al*
Lines D Management of asthma: a consensus statement: correspondence **468**
Littlewood J M *see* Brett M M *et al*
Littlewood J M *see* Simmonds E J *et al*
Walters M P *et al*
Lloyd D A *see* Shanbhogue L K R *et al*
Lloyd D R *see* Kolacek S *et al*
Lloyd-Evans N *see* Sullivan P B *et al*
Loonen J J Groot- *see* Groot-Loonen J J
Loong E P L *see* Sung R Y T *et al*
Lucas A, Baker B A and Cole T J Plasma prolactin and clinical outcome in preterm infants **977**
Brooke O G, Cole T J, Morley R and Bamford M F Food and drug reactions, wheezing, and eczema in preterm infants **411**
and Morley R Early diet in preterm babies and developmental status in infancy: correspondence reply **914**
see also Bishop N J *et al*
Morley R *et al*
Lucas M *see* Reusz G S *et al*
Lucey J F *see* Bier D M *et al*
Lungarella G *see* de Santi M M *et al*
Lunn P G *see* Sullivan P B *et al*
Lutkin J E *see* Davies H *et al*

Mccarthy G *see* Agnarsson U *et al*
Mcclure G European Journal of Pediatrics: sister journal—Europe **1182**
see also Halliday H L and Mcclure G
Mccormick B Early identification of hearing loss: screening and surveillance methods: commentary **484**
see also Wood S and Mccormick B
Macdonald A *see* Williams J *et al*
Macdonald P D, Galea P and Alroomi L G A Catabolic state in dexamethasone treatment of bronchopulmonary dysplasia: correspondence **560**
Walker I D, Galea P and Alroomi L G Acquired transient protein C deficiency in neonatal cardiac failure: correspondence **158**
Mcelwain T J *see* Pinkerton C R *et al*
Mcfadyen A *see* Black D *et al*
Macfadyen U M *see* Hampton F J *et al*
Macfarlane J A *see* Ahmed M L *et al*
Macfaul R *see* Primavesi R and Macfaul R
Mcgaw J *see* Taylor C J *et al*
Mcgenity K G *see* Wilson-Storey D *et al*
Mcgraw M E *see* Moss G D *et al*
Mcintosh N and Mitchell V A clinical trial of two parenteral nutrition solutions in neonates **692** *fn*
Prakash P and Smith A Air leaks and vasopressin release **1259**
Mcintyre S *see* Taylor C J *et al*
Mackay P *see* Hoy C *et al*
Millar M R *et al*
Mackenzie C A, Milner R D G, Bergvall U and Powell T Growth failure secondary to moyamoya syndrome **232**
Mckenzie S A *see* Lear G H *et al*
Levene S and Mckenzie S A

Mclain B I, Davidson P M, Stokes K B and Beasley S W Growth after gut resection for Crohn's disease **760**
Mclelland J, Broadbent V, Yeomans E, Malone M and Pritchard J Langerhans cell histiocytosis: the case for conservative treatment **301**
Macmahon P, Mayne P D, Blair M, Pope C and Kovar I Z Acid-base state of the preterm infant and the formulation of intravenous feeding solutions **354** *fn*
  Calcium and phosphorus solubility in neonatal intravenous feeding solutions **352** *fn*
Mcmaster D J *see* Jewkes F E M *et al*
Mcnally J *see* Bass D H *et al*
Mcnamara J M *see* Hewson P H *et al*
Mcnay M B *see* Swinhoe D J *et al*
Mcneish A S *see* Andrews R *et al*
  Coombs R C *et al*
Mcpherson K *see* Ahmed M L *et al*
Mcveagh P *see* Miller J J *et al*
Magni A *see* de Santi M M *et al*
Magnusson C G M *see* Annerén G *et al*
Mäki M, Holm K, Koskimies S, Hällström O and Visakorpi J K Normal small bowel biopsy followed by coeliac disease **1137**
Main K, Kastrup K W and Skakkebæk N E Reduced sweating in Laron's dwarfism: correspondence **1380**
Malfroot A *see* Toppet M *et al*
Mallett P and Murch S Anorexia nervosa complicating inflammatory bowel disease **298**
Malone M *see* Mclelland J *et al*
Malone P S and Kiely E M Role of aortopexy in the management of primary tracheomalacia and tracheobronchomalacia **438**
Mandal B K *see* Fox R *et al*
Mandini M *see* Cacciari E *et al*
Mann J R *see* Muir K R *et al*
Manning D J, Price W I J and Pearse R G Fetal ascites: an unusual presentation of Niemann-Pick disease type C: correspondence **335**
Mansfield P *see* Chapman B *et al*
Marchand S *see* Saliba E *et al*
Marcovitch H Sore throats: annotation **249**
Marder E, Nicoll A, Polnay L and Shulman C E Discovering anaemia at child health clinics **892**
Maresh M *see* Mohammed T *et al*
Marks V *see* Collins J E *et al*
Marlow N, Ellis A M, Roberts B L and Cooke R W I Five year outcome of preterm sextuplets related to size at birth **451**
  Weindling A M, van Peer A and Heykants J Alfentanil pharmacokinetics in preterm infants **349** *fn*
  see also Rosenbloom L and Marlow N
Marr J *see* Schaefer F *et al*
Marshall L R *see* Minutillo C *et al*
Marti H-P *see* Egger M *et al*
Masera G *see* Politis C *et al*
Mathur A *see* Kumar R *et al*
Matthew D J *see* Davies H *et al*
  Kennedy J D *et al*
Matthews G *see* Russell J G B *et al*
Matthews J N S *see* Scott J E S *et al*
Mäusezahl D *see* Egger M *et al*
May B *see* Gibb D M *et al*
Mayne A J, Handy D J, Preece M A, George R H and Booth I W Dietary management of D-lactic acidosis in short bowel syndrome **229**
Mayne P D *see* Macmahon P *et al*
Mazzoleni S *see* da Dalt L *et al*
Meer S B van der *see* van der Meer S B
Meghji S *see* Gibbs J *et al*
Meller S T *see* Pinkerton C R *et al*
Mellor D H *see* Elias-Jones A C *et al*
Messaritakis J, Anagnostakis D, Laskari H and Katerelos C Rectal-skin temperature difference in septicaemic newborn infants **380** *fn*
Metzger B E, Silverman B L, Freinkel N, Dooley S L, Ogata E S and Green O C Amniotic fluid insulin concentration as a predictor of obesity **1050** *fn*
Michie C A Collecting 24 hour urine samples from children: correspondence **1184**
  and Raffles A Iron supplementation in the preterm or low birthweight infant: correspondence **559**
Middleton G W *see* Powell K *et al*
Middleton J *see* Hall D M B *et al*
Midgley P C, Azzopardi D, Oates N, Shaw J C L and Honour J W Virilisation of female preterm infants **701** *fn*
Mieli-Vergani G *see* Hadžić N *et al*
Miles M *see* Richman S and Miles M
Milford D V and Taylor C M New insights into the haemolytic uraemic syndromes: annotation **713**
  Guttridge B, Hall S M, Rowe B and Kleanthous H Haemolytic uraemic syndromes in the British Isles 1985–8: association with Verocytotoxin producing *Escherichia coli*. Part 1: clinical and epidemiological aspects **716**
  see also Kleanthous H *et al*
Milla P *see* Kent A *et al*
Milla P J Reflux vomiting: current topic **996**
  see also Hill S M and Milla P J
  Sokel B S *et al*
Millar M R, Todd N and Mackay P Neonatal infections with coagulase negative staphylococci: annotation **1015** *fn*
  see also Hoy C *et al*
Miller E Rubella reinfection: annotation **820**
Miller J J, Brand J C and Mcveagh P Breath hydrogen excretion in infants with colic: correspondence **248**
Miller P F W, Bowmer C J, Wheeldon J and Brocklebank J T Pharmacokinetics of prednisolone in children with nephrosis **196**
Milligan D W A *see* Wariyar U K *et al*
Mills A F Surveillance for anaemia: risk factors in patterns of milk intake **428**
Milner A D Lung function testing in infancy: current topic **548**
  see also Chapman B *et al*
  Davies F A *et al*
  Everard M and Milner A D
  O'Callaghan C *et al*
  Priftis K *et al*
Milner R D G Proper use of growth hormone: annotation **70**
  see also Mackenzie C A *et al*
Minutillo C, Pemberton P J, Willoughby M L N, Price P J and Marshall L R Neonatal purpura fulminans and transient protein C deficiency: correspondence **561**
Mitchell C D *see* Onadim Z O *et al*
Mitchell E A International trends in postneonatal mortality **607**
  and Anderson H R Changes in asthma prevalence: correspondence **646**
Mitchell V *see* Mcintosh N and Mitchell V
Mohammed T, Maresh M, Sibley C P and Boyd R D H Absent maternofetal potassium gradient at term **384** *fn*
Mok J Y Q and Yap P L Intravenous immunoglobulin in HIV infection: correspondence reply **248**
  see also Hague R A *et al*
Molenaar J C *see* Bos A P *et al*
Moll H A van Steensel- *see* van Steensel-Moll H A
Moncrieff M W Life threatening illness and hospice care: correspondence **468**
Montalembert M de *see* de Montalembert M
Montini G *see* da Dalt L *et al*
Moorthy B, Colditz P R, Ives K N, Rees D G, Van't Hoff W G and Hope P L Reproducibility of cerebral artery Doppler measurements **700** *fn*
Moran D J *see* Spencer J A D *et al*
Morgan D W *see* Blake K D *et al*
Morgan G *see* Finn A *et al*
Morgan J D *see* Andrews R *et al*
Morgan M E I *see* Coombs R C *et al*
Morgese G *see* Chairelli F *et al*
Morley C J and Morley R Follow up of premature babies treated with artificial surfactant (ALEC) **667** *fn*
  Thornton A J, Fowler M A, Cole T J and Hewson P H Respiratory rate and severity of illness in babies under 6 months old **834**
  see also Thornton A J *et al*
Morley R, Brooke O G, Cole T J, Powell R and Lucas A Birthweight ratio and outcome in preterm infants **30** *fn*
  see also Lucas A *et al*
  Lucas A and Morley R
  Morley C J and Morley R
  Readett D R J *et al*
Morris J S *see* Readett D R J *et al*
Morris K *see* Lambert H *et al*
Morris-Jones P H and Craft A W Childhood cancer: cure at what cost?: current topic **638**
  see also Groot-Loonen J J *et al*
Morrissey M S C and Bailey C M Diagnosis and management of subglottic stenosis after neonatal ventilation: annotation **1103**
Morton N S *see* Kinmond S *et al*
Moseley M J *see* Robinson J *et al*
Moss A L H, Jones K and Pigott R W Submucous cleft palate in the differential diagnosis of feeding difficulties **182**
Moss G D, Primavesi R J, Mcgraw M E and Chambers T L Correction of hypernatraemia with continuous arteriovenous haemodiafiltration: short report **628**
Mota H C da *see* da Mota H C
Mott M G *see* Foot A B M *et al*
Mount G E *see* Russell J G B *et al*
Mowat A P *see* Hadžić N *et al*
  Noble-Jamieson *et al*
Moxon E R *Haemophilus influenzae* infections in siblings: the need for prophylaxis: commentary **490**
Moya F R, Grannum P A T, Riddick L, Robert J A and Pinheiro J Atrial natriuretic factor in hydrops fetalis caused by Rh isoimmunisation **683** *fn*

Muir K R, Huddart S N, Barrantes J, Parkes S E and Mann JR Relative occurrence of neuroblastoma and Wilms' tumour in ethnic subgroups in the West Midlands Health Authority Region: correspondence **1380**
Smith H, Parkes S E, Willshaw H, Harry J, Mann J R and Stevens M C G Increasing incidence of retinoblastoma?: correspondence **915**
Murdoch I A and dos Anjos R Continued need for pneumococcal prophylaxis after splenectomy **1268**
Murphy G H *see* Kent A *et al*
Murphy J *see* Ahmed F *et al*
Murch S Effect of fever on recurrence rate of febrile convulsions: correspondence **333**
see also Mallett P and Murch S
Murphy M S, Eastham E J, Nelson R and Aynsley-Green A Non-invasive assessment of intraluminal lipolysis using a $^{13}CO_2$ breath test **574**
Musumeci S *see* Leonardi S *et al*

Najean Y *see* de Montalembert M *et al*
Napier W A *see* Jewkes F E M *et al*
Natalini G *see* Catassi C *et al*
Nazer H *see* Ichimiya H *et al*
Neale G *see* Sullivan P B *et al*
Neijens H J *see* van Steensel-Moll H A *et al*
Nelson E A S *see* Williams S M *et al*
Nelson R *see* Murphy M S *et al*
Newman C L, Barton C and Ryder H Palliative care for children with cancer: correspondence **1378**
Ng P C, Thomson M A and Dear P R F Dexamethasone and infection in preterm babies: a controlled study **54** *fn*: correspondence reply **812**
Ng W K, Taylor N F, Hughes I A, Taylor J, Ransley P G and Grant D B 5α-Reductase deficiency without hypospadias **1166**
see also Yeung C K *et al*
Nibhrolchain C *see* Austin R P and Nibhrolchain C
Nicolaides K *see* Thompson P J *et al*
Nicolini U *see* Fisk N M *et al*
Nicoll A Research in community child health: correspondence **158**
see also Marder E *et al*
Niese D *see* Wagner N *et al*
Ninan G *see* Shanbhogue L K R *et al*
Noble-Jamieson G, Barnes N D, Thiru S and Mowat A P Severe hypertension after liver transplantation in alpha$_1$ antitrypsin deficiency **1217**
Nordvall S L *see* Annerén G *et al*
Northover B N *see* Hodges S *et al*
Northway W H Bronchopulmonary dysplasia: then and now: current topic **1076** *fn*
Nylén O *see* Trollfors B *et al*

Oakhill A *see* Foot A B M *et al*
Oates N *see* Midgley P C *et al*
O'Callaghan C, Milner A D and Swarbrick A Nebulised sodium cromoglycate in infancy: airway protection after deterioration **404**
see also Barlow J *et al*
Chapman B *et al*
O'Cathain C *see* Devlin J B and O'Cathain C
Odermatt P *see* Egger M *et al*
O'Donnell T V *see* Shaw R A *et al*
Offner G *see* Gordjani N *et al*
Offringa M *see* van Steensel-Moll H A *et al*
Ogata E S *see* Metzger B E *et al*
O'Malley B P *see* Hodges S *et al*
Onadim Z O, Mitchell C D, Rutland P C, Buckle B G, Jay M, Hungerford J L, Harper K and Cowell J K Application of intragenic DNA probes in prenatal screening for retinoblastoma gene carriers in the United Kingdom **651** *fn*
Oslizlok P *see* Case C L *et al*

Paediatric training, postgraduate, Organising Committee for Workshop Postgraduate training in Europe for the next decade: medical education **644**
Page A C, Price J F, Salisbury J R, Howard E R and Karani J Chronic intussusception **134**
Paladini D, Chita S K and Allan L D Prenatal measurement of cardiothoracic ratio in evaluation of heart disease **20** *fn*
Palm D G *see* Kurlemann G and Palm D G
Palma A di *see* di Palma A
Paludetto R *see* Greco L *et al*
Panday S *see* Conway S P *et al*
Pandey S K *see* Knights B and Pandey S K
Pandov H *see* Williams J *et al*
Parish H *see* Gibb D M *et al*
Parkes S E *see* Muir K R *et al*
Parkin A and Brocklebank J T Which routine test for kidney function: correspondence reply **561**
Parkin J M *see* Edwards A G K *et al*
Platt M P W and Parkin J M
Welbury J *et al*
Parton J *see* Jackson S K *et al*
Pasi K J, Collins M A, Ewer A K and Hill F G H Growth in haemophilic boys after HIV infection **115**
Paynter A *see* Jarvis S N *et al*
Welbury J *et al*
Pearse R G *see* Manning D J *et al*
Pearson A D J *see* Skinner R *et al*
Pedersen S, Hansen O R and Fuglsang G Influence of inspiratory flow rate upon the effect of a Turbuhaler **308**
Peer A van *see* van Peer A
Pemberton P J *see* Minutillo C *et al*
Pembrey M *see* Reardon W and Pembrey M
Pendergast A *see* Selikowitz M *et al*
Pendray M R *see* Foote K D *et al*
Penna G la *see* la Penna G
Perelstein E M, Grunfeld B G, Simsolo R B, Gimenez M I and Gianantonio C A Renal functional reserve compared in haemolytic uraemic syndrome and single kidney **728**
Perry R H *see* Wariyar U K *et al*
Petersen S A *see* Anderson E S *et al*
Rawson D *et al*
Wailoo M P *et al*
Pharoah P O D Impairment, disability, and handicap: annotation **819**
Incidence and prevalence: annotation **471**
and Alberman E D Annual statistical review **147**
Cooke T, Cooke R W I and Rosenbloom L Birthweight specific trends in cerebral palsy **602**
Phillips G, Forsyth J S and Harper I A Diagnosis of neonatal chlamydial conjunctivitis **894**
Phillips R R *see* Conway S P *et al*
Pigott R W *see* Moss A L H *et al*
Pillai M and James D Behavioural states in normal mature human fetuses **39** *fn*
Hiccups and breathing in human fetuses **1072** *fn*
Pinheiro J *see* Moya F R *et al*
Pinkerton C R, Williams D, Wootton C, Meller S T and McElwain T J 5-HT$_3$ antagonist ondansetron—an effective outpatient antiemetic in cancer treatment **822**
see also Groot-Loonen J J *et al*
Pipkin F B *see* Stephenson T J and Pipkin F B
Pippard M J *see* Earley A *et al*
Pirazzoli P *see* Cacciari E *et al*
Platt M P W and Parkin J M Performance appraisal and career counselling for senior house officers: medical education **796**
Poets C F *see* Samuels M P *et al*
Politis C, di Palma A, Fisfis M, Giasanti A, Richardson S C, Vullo C and Masera G Social integration of the older thalassaemic patient **984**
Pollock I and Warner J O Effect of artificial food colours on childhood behaviour **74**
Polnay L *see* Marder E *et al*
Pope C *see* MacMahon P *et al*
Porteous L E *see* Shaw R A *et al*
Porter J D H, Robinson P H, Glasgow J F T, Banks J H and Hall S M Trends in the incidence of Reye's syndrome and the use of aspirin **826**
Portmann B *see* Hadžić N *et al*
Postlethwaite R J *see* Jewkes F E M *et al*
Lewis M A *et al*
Powell A *see* Smith G C *et al*
Powell K, Middleton G W and Forster G E *Chlamydia trachomatis* in infants: a prospective study: correspondence **336**
Powell R *see* Morley R *et al*
Powell T *see* Mackenzie C A *et al*
Prakash P *see* McIntosh N *et al*
Preece M A *see* Mayne A J *et al*
Puntis J W L *et al*
Rees L *et al*
Preece P M, Anderson J M and Thompson R G *Chlamydia trachomatis* in infants: a prospective study: correspondence reply **336**
Price A B *see* Sundaresan M *et al*
Price C E *see* Gulliford M C *et al*
Price D A, Addison G M and Herbert E D Increase in urinary growth hormone excretion in puberty **1203**
see also Crowne E C *et al*
Price J F *see* Page A C *et al*
Price L *see* Skinner R *et al*
Price P J *see* Minutillo C *et al*
Price W I J *see* Manning D J *et al*
Priestley B L and Bleehen S S Lichen sclerosus and sexual abuse: correspondence **335**
Priftis K, Milner A D, Conway E and Honour J W Adrenal function in asthma **838**
Primavesi R and Macfaul R Paediatric medical audit: current topic **1170**

Primavesi R J *see* Moss G D *et al*
Primhak R A *see* Wales J K H *et al*
Pritchard J *see* Gibbs J *et al*
  Groot-Loonen J J *et al*
  Mclelland J *et al*
Puntis J W L, Ball P A and Preece M A Egg and breast milk based nitrogen sources compared: correspondence reply **337**
  Ritson D G, Holden C E and Buick R G Growth and feeding problems after repair of oesophageal atresia **84**
  Tarlow M J, Raafat F and Booth I W Crohn's disease of the lung **1270**
  see also Kolacek S *et al*

Raafat F *see* Puntis J W L *et al*
Radhi A S El- *see* El-Radhi A S
Radinger H *see* Wagner N *et al*
Raffles A *see* Michie C A and Raffles A
Ralston C and Butt W Continuous vasopressin replacement in diabetes insipidus **896**
Ransley P G *see* Ng W K *et al*
Rascher C *see* Schofer O *et al*
Ratcliffe J M *see* Blake K D *et al*
Rätsch I M *see* Catassi C *et al*
Rattenbury J *see* Wales J K H *et al*
Ravindranath C *see* Blackwell P *et al*
Rawson D, Petersen S A and Wailoo M P Rectal temperature of normal babies the night after first diphtheria, pertussis, and tetanus immunisation **1305**
Raymond D R *see* Irving W L *et al*
Rayner R J, Hiller E J, Ispahani P and Baker M Haemophilus infection in cystic fibrosis **255**
Readett D R J, Morris J S and Serjeant G R Nocturnal enuresis in sickle cell haemoglobinopathies **290**
  Determinants of nocturnal enuresis in homozygous sickle cell disease **615**
Reardon W and Pembrey M The genetics of deafness: annotation **1196**
Redington A and Bush A Fragile X mental retardation: correspondence **335**
Redmond A O B *see* Wilson D C and Redmond A O B
Rees D G *see* Moorthy B *et al*
Rees L, Rigden S P A, Ward G and Preece M A Treatment of short stature in renal disease with recombinant human growth hormone **856**
Reid M M Serum immunoglobulins in acute lymphoblastic leukaemia: correspondence **1379**
Reijnen J A M, Festen C and van Roosmalen R P Intussusception: factors related to treatment **871**
Rennie J *see* Gandy G and Rennie J
Rennie J M Transcutaneous carbon dioxide monitoring: annotation **345** *fn*
  see also Bishop N J *et al*
Reusz G S, Hoyer P F, Lucas M, Krohn H P, Ehrich J H H and Brodehl J X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis **1125**
Revillon Y *see* de Montalembert M *et al*
Reynolds K *see* Smith G C *et al*
Richards S *see* Chessells J M *et al*
Richardson R J and Kirk J M W Short stature, mental retardation, and hypoparathyroidism: a new syndrome **1113**
Richardson S C *see* Politis C *et al*
Richman S and Miles M Selective medical examinations for school entrants: the way forward: personal view **1177**
Riddick L *see* Moya F R *et al*
Rigden S P A *see* Rees L *et al*
Rigo J *see* de Curtis M *et al*
Rimmer S *see* Wallace G *et al*
Ritson D G *see* Puntis J W L *et al*
Rivlin E *see* Sinha S K *et al*
Robb L G and Tiedeman K Idiopathic thrombocytopenic purpura: predictors of chronic disease **502**
Robert J A *see* Moya F R *et al*
Roberton D M *see* Hewson P H *et al*
  Sennhauser F H *et al*
Roberts B L *see* Marlow N *et al*
Roberts D S, Haycock G B, Dalton R N, Turner C, Tomlinson P, Stimmler L and Scopes J W Prediction of acute renal failure after birth asphyxia **1021** *fn*
Roberts J P and Burge D M Antenatal diagnosis of abdominal wall defects: a missed opportunity? **687** *fn*
Roberts-Harry J, Green S H and Willshaw H E Optic nerve hypoplasia: associations and management **103**
Robertson C F *see* Freezer N J *et al*
Robinson J and Fielder A R Pupillary diameter and reaction to light in preterm neonates **35** *fn*
  Moseley M J and Fielder A R Illuminance of neonatal units **679** *fn*
Robinson M J *see* Hewson P H *et al*
  Williamson J B *et al*
Robinson P H *see* Porter J D H *et al*
Robinson P J and Sly P D High dose pancreatic enzymes in cystic fibrosis **311**
Robinson R O Ventilator dependency in the United Kingdom **1235**
Roche A F *see* Himes J H and Roche A F
Rode H *see* Bass D H *et al*
Rodeck C H *see* Fisk N M *et al*
Rogers D I *see* Freeman W *et al*
Rogers M Terminology in community child health—an urgent need for consensus?: correspondence **1287**
Rogers P *see* Appleton R E *et al*
Rolles C J *see* Hall M A *et al*
Rona R J *see* Gulliford M C *et al*
Roome A P C H *see* Das B D *et al*
Roosmalen R P van *see* van Roosmalen R P
Rosenbloom L and Marlow N Teaching junior staff about caring for handicapped children: medical education **903**
  see also Pharoah P O D *et al*
Ross H *see* Simmonds E J *et al*
Ross O *see* Kyle D *et al*
Rossini M *see* Catassi C *et al*
Rothera M *see* Franks R and Rothera M
Rowe B *see* Kleanthous H *et al*
  Milford D V *et al*
Roy S K, Haider R, Akbar M S, Alam A N, Khatun M and Eeckels R Persistent diarrhoea: clinical efficacy and nutrient absorption with a rice based diet **294**
Russell G The Royal Aberdeen Children's Hospital: 'Hospital of the year 1989': current topic **900**
Russell J G B, Matthews G and Mount G E Ozone in medical gases: correspondence **1185**
Russell R I R and Helms P J Audit—where do we go from here?: annotation **1107**
Russell-Eggitt I M *see* Blake K D *et al*
Rutland P C *see* Onadim Z O *et al*
Ryan S W, Forsythe I, Hartley R, Haworth M and Bowmer C J Slow release carbamazepine in treatment of poorly controlled seizures **930**
  see also Congdon P J *et al*
Ryder H *see* Newman C L *et al*
Rylance G W *see* Houtman P N *et al*

Saene H K F van *see* van Saene H K F
Saing H *see* Yeung C K *et al*
Saliba E, Bertrand P, Gold F, Marchand S and Laugier J Area of lateral ventricles measured on cranial ultrasonography in preterm infants: association with outcome **1033** *fn*
  Vaillant M C and Laugier J Area of lateral ventricles measured on cranial ultrasonography in preterm infants: reference range **1029** *fn*
Salisbury J R *see* Page A C *et al*
Salmon B, Wilson N M and Silverman M How much aerosol reaches the lungs of wheezy infants and toddlers? **401**
Samuels M P, Poets C F and Southall D P Monitoring and sudden infant death syndrome: correspondence **913**
  see also Southall D P and Samuels M P
  Southall D P *et al*
San Lazaro C Lichen sclerosus: correspondence **1184**
Santi M M de *see* de Santi M M
Sapiano S B *see* Freeman W *et al*
Sartori P C E, Gordon G J and Darbyshire P J Continuous papaveretum infusion for the control of pain in painful sickling crisis **1151**
Scalise F *see* Bertotto A *et al*
Scanlon P E and Bamford J M Early identification of hearing loss: screening and surveillance methods **479**
Schaefer F, Marr J, Seidel C, Tilgen W and Schärer K Assessment of gonadal maturation by evaluation of spermaturia **1205**
Schärer K *see* Schaefer F *et al*
Schofer O, Beetz R, Kruse K, Rascher C, Schütz C and Bohl J Nephrogenic diabetes insipidus and intracerebral calcification **885**
Scholey S *see* Emery J L *et al*
Schneweis K E *see* Wagner N *et al*
Schütz C *see* Schofer O *et al*
Schwarz H P and Duck S C Growth hormone deficiency in children with chromosomal abnormalities: correspondence **334**
Sciacca A *see* Leonardi S *et al*
Scobie W G *see* Wilson-Storey D *et al*
Scopes J W *see* Roberts D S *et al*
Scotland S M *see* Kleanthous H *et al*
Scott J E S, Hunter E W, Lee R E J and Matthews J N S Ultrasound measurement of renal size in newborn infants **361** *fn*
Scrimgeour A *see* Usherwood T P *et al*
Seddon P C and Heaf D P Long term outcome of ventilated asthmatics **1324**
Seidel C *see* Schaefer F *et al*
Selikowitz M, Sunman J, Pendergast A and Wright S Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial **112**
Sennhauser F H, Balloch A, Shelton M J, Doyle L W, Yu V Y H and Roberton D M Immunoglobulin and anti- *Escherichia coli* antibody in

lower respiratory tract secretions from infants weighing less than 1500 g at birth **48** *fn*
Senterre J *see* de Curtis M *et al*
Serjeant G R *see* Readett D R J *et al*
Seshia S S, Derbyshire G, Haworth J C and Hoogstraten J Myopathy with hypophosphatasia **130**
Sethi G D *see* Kumar R *et al*
Sever P S *see* Deal J E *et al*
Seward D *see* Goulder P *et al*
Shah V *see* Deal J E *et al*
Shalet S M *see* Crowne E C *et al*
Shanbhogue L K R, Tam P K H, Ninan G and Lloyd D A Preoperative stabilisation in congenital diaphragmatic hernia **1043** *fn*
Sharma S *see* Kumar R *et al*
Sharp J *see* Lambert H *et al*
Shaw J C L *see* Midgley P C *et al*
Shaw N J and Dear P R F How do parents of babies interpret qualitative expressions of probability? **520**: correspondence reply **1379**
  Wheeldon J and Brocklebank J T Indices of intact serum parathyroid hormone and renal excretion of calcium, phosphate, and magnesium **1208**
  see also Thomas H N *et al*
Shaw R A, Crane J, O'Donnell T V, Porteous L E and Coleman E D Increasing asthma prevalence in a rural New Zealand adolescent population: 1975–89 **1319**
Shelton M J *see* Sennhauser F H *et al*
Sheppard M *see* Bowyer J J and Sheppard M
Sheps S *see* Foote K D *et al*
Shieh C-C, Chang M-H and Chen C-L Dubin-Johnson syndrome presenting with neonatal cholestasis **898**
Shield L K *see* Kiers L *et al*
Shinebourne E A *see* Bowyer J J *et al*
    Bush A *et al*
Short A Antibiotic treatment of suspected neonatal meningitis: correspondence **810**
Shortland G *see* Jackson S K *et al*
Shulman C E *see* Marder E *et al*
Shuper A, Vining E P G and Freeman J M Central nervous system vasculitis after chickenpox—cause or coincidence? **1245**
Sibley C P *see* Mohammed T *et al*
Sikka S *see* Blackwell P *et al*
Silva P de *see* de Silva P
Silverman B L *see* Metzger B E *et al*
Silverman M Aerosol therapy in the newborn: workshop report **906**
  Self management plans for asthma: correspondence **333**
  see also Davies P A *et al*
    Salmon B *et al*
    Wilson N M and Silverman M
Simmonds E J, Conway S P, Ghoneim A T M, Ross H and Littlewood J M *Pseudomonas cepacia*: a new pathogen in patients with cystic fibrosis referred to a large centre in the United Kingdom **874**
  Littlewood J M and Evans E G V Cystic fibrosis and allergic bronchopulmonary aspergillosis **507**
Simpson H *see* Caswell S J *et al*
    Davies P A *et al*
    Hampton F J *et al*
    Thomson A H *et al*
Sims D G *see* Gladman G *et al*
Simsolo R B *see* Perelstein E M *et al*
Sinha S *see* Asthana J C *et al*
    de Silva P *et al*
    Gladman G *et al*
Sinha S K, D'souza S W, Rivlin E and Chiswick M L Ischaemic brain lesions diagnosed at birth in preterm infants: clinical events and developmental outcome **1017** *fn*
Sixt R *see* Krantz I *et al*
Sjövall J *see* Ichimiya H *et al*
Skakkebæk N E *see* Main K *et al*
Skeoch C H *see* Kinmond S *et al*
Skinner R, Pearson A D J, Price L, Coulthard M G and Craft A W Nephrotoxicity after ifosfamide **732**
Skoner D P and Fireman P Increases in plasma concentrations of a prostaglandin metabolite in acute airway obstruction: correspondence reply **560**
Sly P D *see* Robinson P J and Sly P D
Small P *see* Chapman B *et al*
Smith A *see* McIntosh N *et al*
Smith G C, Powell A, Reynolds K and Campbell C A The five year school medical—time for change **225**
Smith H *see* Muir K R *et al*
Smith H C *see* Wallace G *et al*
Smith H R *see* Kleanthous H *et al*
Smith I Egg and breast milk based nitrogen sources compared: correspondence **336**
  Beasley M G and Ades A E Intelligence and quality of dietary treatment in phenylketonuria **472**
Smith J A Walker- *see* Walker-Smith J A
Smith P Grattan- *see* Grattan-Smith P
Smith S L *see* Hall M A *et al*
So L Y *see* Fok T F *et al*
Sokel B S, Devane S P, Bentovim A and Milla P J Self hypnotherapeutic treatment of habitual reflex vomiting **626**
Southall D P and Samuels M P Bronchopulmonary dysplasia: a new look at management: personal practice **1089** *fn*
  and Talbert D G Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death **953**
  see also Samuels M P *et al*
Spehl M *see* Toppet M *et al*
Speight N *see* Fletcher H J *et al*
Spencer J A D, Moran D J, Lee A and Talbert D White noise and sleep induction **135**
Spranger J *see* Bier D M *et al*
Sreeram N and Wren C Supraventricular tachycardia in infants: response to initial treatment **127**
Staines A Dexamethasone and infection in preterm babies: a controlled study: correspondence **812**
Stalker C R *see* Freeman W *et al*
Stark J M *see* Jackson S K *et al*
Steensel-Moll H A van *see* van Steensel-Moll H A
Stein A, Forrest G C, Woolley H and Baum J D Life threatening illness and hospice care: correspondence reply **468**
Stephenson T J and Pipkin F B Atrial natriuretic factor: the heart as an endocrine organ: annotation **1293**
Stevens M C G *see* Muir K R *et al*
Stewart G and Farmer G Sturge-Weber and Klippel-Trenauny syndromes with absence of inferior vena cava **546**
Stibler H and Jaeken J Carbohydrate deficient serum transferrin in a new systemic hereditary syndrome **107**
Stijnen T *see* Bos A P *et al*
Stiller C A *see* Levitt G A *et al*
Stimmler L *see* Roberts D S *et al*
Stokes K B *see* McLain B I *et al*
Stone D H Terminology in community child health—an urgent need for consensus: annotation **817**
Stonehouse M *see* Kyle D *et al*
Storey D Wilson- *see* Wilson-Storey D
Strachan D P Do chesty children become chesty adults? annotation **161**
Strang, Professor Leonard B; James Spence Medallist, 1990 **1101**
Strang S *see* Gibb D M *et al*
Strangert K *see* Trollfors B *et al*
Strobel S *see* Finn A *et al*
Sullivan P B, Thomas J E, Eastham E J, Lunn P G and Neale G *Helicobacter pylori* and protein losing enteropathy: correspondence **332**
  Wight D G D, Neale G, Eastham E J, Corrah T, Lloyd-Evans N and Greenwood B M *Helicobacter pylori* in Gambian children with chronic diarrhoea and malnutrition **189**
Sundaresan M, Wright M and Price A B Anatomy and development of the fontanelle **386** *fn*
Sunderland R *see* Kyle D *et al*
Sung R Y T, Yin J A, Loong E P L, Fok T F and Lau J Topical prostaglandin E_2 gel for cervical ripening and closure of the ductus arteriosus in the newborn **703** *fn*
Sunman J *see* Selikowitz M *et al*
Supramaniam G *see* Winrow A P and Supramaniam G
Suzuki A, Tizard E J, Gooch V, Dillon M J and Haworth S G Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom **1142**
Swanton R H *see* John R M *et al*
Swarbrick A *see* O'Callaghan C *et al*
Swift P G F *see* Hodges S *et al*
Swinhoe D J, Gilmore D H, McNay M B and Whittle M J Rh haemolytic disease: continuing problem of management **365** *fn*

Talbert D *see* Spencer J A D *et al*
Talbert D G *see* Southall D P *et al*
Talbot J F *see* Huggon I C *et al*
Tam P K H and Angeleri E M T Is low serum alpha fetoprotein a sensitive marker for diaphragmatic hernia?: correspondence **912**
  see also Shanbhogue L K R *et al*
Tamhne R C, Jarvis S N and Waterston A J R Auditing community screening for undescended testes **888**
Tanner M *see* Egger M *et al*
Tannirandorn Y *see* Fisk N M *et al*
Tarlow M J Antibiotic treatment of suspected neonatal meningitis: correspondence **810**
  see also Puntis J W L *et al*
Tatman M A Purchasers, providers, and community paediatricians: correspondence **1183**
Tayler P J *see* Clark A F *et al*
Taylor B *see* Bevis M and Taylor B
Taylor B J *see* Williams S M *et al*

Taylor C J, Mcgaw J, Howden R, Duerden B I and Baxter P S Bacterial reservoirs in cystic fibrosis **175**
  Mcintyre S and Baxter P S Nutrition in cystic fibrosis: correspondence **646**
  see Wales J K H *et al*
Taylor C M *see* Kleanthous H *et al*
  Milford D V *et al*
  Milford D V and Taylor C M
Taylor D *see* Holmström G *et al*
  Kaur B and Taylor D
Taylor E M and Emery J L Categories of preventable unexpected infant deaths **535**
  see also Emery J L *et al*
Taylor J *see* Ng W K *et al*
Taylor J F N Natural and modified history of complete atrioventricular septal defect—a 17 year study: commentary **966**
Taylor J W *see* Gilbertson N J *et al*
Taylor N F *see* Ng W K *et al*
Teale D *see* Collins J E *et al*
Temple K *see* Holmström G *et al*
Thalayasingam B *see* Banton C R *et al*
Thiru S *see* Noble-Jamieson G *et al*
Thomas H M, Shaw N J and Weindling A M Generalised lymphangiomatosis with chylothorax: correspondence **334**
Thomas J E *see* Sullivan P B *et al*
Thompson E N *see* Jackson S K *et al*
Thompson N L *see* Boland C and Thompson N L
Thompson P J, Greenhough A and Nicolaides K Chronic respiratory morbidity after prolonged and premature rupture of the membranes **878**
Thompson R G *see* Preece P M *et al*
Thomson A H, Beardsmore C S, Firmin R, Leanage R and Simpson H Airway function in infants with vascular rings: preoperative and postoperative assessment **171**
  see Caswell S J *et al*
Thomson M A *see* Ng P C *et al*
Thormar H *see* Isaacs C E *et al*
Thornton A J, Morley C J, Hewson P H, Cole T J, Fowler M A and Tunnacliffe J M Symptoms in 298 infants under 6 months old, seen at home **280**
  see also Morley C J *et al*
Tibbling L *see* Gustafsson P M *et al*
Tibboel D *see* Bos A P *et al*
Tiedeman K *see* Robb L G and Tiedeman K
Tilgen W *see* Schaefer F *et al*
Till J A *see* Bowyer J J *et al*
Timms C *see* Clark B J *et al*
Tissing W J E *see* van Steensel-Moll H A *et al*
Tizard E J *see* Suzuki A *et al*
Todd N *see* Millar M R *et al*
Tomlinson L *see* Bradford R and Tomlinson L
Tomlinson P *see* Roberts D S *et al*
Toppet M, Malfroot A, Derde M P, Toppet V, Spehl M and Dab I Corticosteroids in primary tuberculosis with bronchial obstruction **1222**
Toppet V *see* Toppet M *et al*
Trevisan C *see* Cacciari E *et al*
Trollfors B, Nylén O and Strangert K Acute epiglottitis in children and adults in Sweden 1981–3 **491**
Trollfors B *see* Krantz I *et al*
Trompeter R S Renal transplantation: current topic **143**
Truscott J G *see* Congdon P J *et al*
Tsang S S *see* Fok T F *et al*
Tsang T M *see* Yeung C K *et al*
Tunnacliffe J M *see* Thornton A J *et al*
Turner C *see* Roberts D S *et al*
Turner T *see* Hudson I *et al*
Turner T L *see* Hudson I R B *et al*

Ueda N, Kuno K and Ito S Eight and 12 week courses of cyclophosphamide in nephrotic syndrome **1147**
Underhill S *see* Hopkins C S *et al*
Usherwood T P, Scrimgeour A and Barber J H Questionnaire to measure perceived symptoms and disability in asthma **779**

Vaccaro R *see* Bertotto A *et al*
Vaillant M C *see* Saliba E *et al*
Valletta E A *see* de Santi M M *et al*
Valman H B *see* Bier D M *et al*
  Earley A *et al*
van der Meer S B, Forget P P and Arends J W Abnormal small bowel permeability and duodenitis in recurrent abdominal pain **1311**
van der Voort E *see* van Steensel-Moll H A *et al*
van Peer A *see* Marlow N *et al*
van Roosmalen R P *see* Reijnen J A M *et al*
van Saene H K F *see* Dalzell A M *et al*
van Steensel-Moll H A, Tissing W J E, Offringa M and Hazelzet J A Mechanical ventilation and respiratory syncytial virus infection: correspondence **332**
van Steensel-Moll H A, Hazelzet J A, ven der Voort E, Neijens H J and Hackeng W H L Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus **1237**
Van't Hoff W G *see* Moorthy B *et al*
Vaughan J P *see* Victora C G *et al*
Ventriculomegaly trial group Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation **3** *fn*
Verber I G and Bain M Glucose polymer regimens and hypernatraemia **627**
Vergani G Mieli- *see* Mieli-Vergani G
Victora C G, Huttly S R A, Barros F C and Vaughan J P Caesarean section and duration of breast feeding among Brazilians **632**
Vining E P G *see* Shuper A *et al*
Visakorpi J K *see* Mäki M *et al*
Voort E van der *see* van der Voort E
Voss L D, Bailey B J R, Cumming K, Wilkin T J and Betts P R The reliability of height measurement (The Wessex Growth Study) **1340**
Vullo C *see* Politis C *et al*

Wagner N, Bialek R, Radinger H, Becker M, Schneweis K E, Brackmann H H and Niese D HIV-1 infection in a cohort in haemophilic patients **1301**
Wailoo M P, Petersen S A and Whitaker H Disturbed nights and 3–4 month old infants: the effects of feeding and thermal environment **499**
  see also Anderson E S *et al*
  Rawson D *et al*
Wales J K H, Primhak R A, Rattenbury J and Taylor C J Isolated fructose malabsorption **227**
Walker C H M On central nervous system investigation (1961)—incidence and development of hydrocephalus: neonatology—then and now **246**
  On plasma volume changes in the newborn (1958/59): neonatology—then and now **331**
Walker I D *see* Macdonald P D *et al*
Walker J and Cudmore R E Respiratory problems and cystic adenomatoid malformation of lung: annotation **649** *fn*
Walker J M, Wood P J, Williamson S, Betts P R and Evans A J Urinary growth hormone excretion as a screening test for growth hormone deficiency 89: correspondence reply **811**
Walker K, Gunn A J and Gluckman P D XO/XY mosaicism in phenotypic males **891**
Walker-Smith J A Management of infantile gastroenteritis: annotation **917**
Wallace G, Smith H C, Watson G H, Rimmer S and D'souza S W Tuberous sclerosis presenting with fetal and neonatal cardiac tumours **377** *fn*
Wallace W H B *see* Crowne E C *et al*
Walters M P, Kelleher J, Gilbert J and Littlewood J M Clinical monitoring of steatorrhoea in cystic fibrosis 99: correspondence reply **913**
Ward G *see* Rees L *et al*
Ward P *see* Bishop N J *et al*
Warde C *see* Agnarsson U *et al*
Wardrop C A J *see* Hudson I *et al*
Wariyar U K, Welch R J, Milligan D W A and Perry R H Sonographic and pathological features of callosal hypoplasia in non-ketotic hyperglycinaemia **670** *fn*
Warner J O Management of asthma: a consensus statement: correspondence reply **468**
Warner J O *see* Pollock I and Warner J O
Waterston A *see* Jarvis S N *et al*
Waterston A J R, Aynsley-Green A, Weaver L T and Whitehead R G Michael Parkin—an international paediatrician: contemporary history **802**
  see also Edwards A G K *et al*
  Tamhne R C *et al*
Watkin P M, Baldwin M and Laoide S Parental suspicion and identification of hearing impairment **846**
Watling R M *see* Davidson D C and Watling R M
Watson B E *see* Das B D *et al*
Watson G H *see* Wallace G *et al*
Weaver L T *see* Waterston A J R *et al*
Webb D K H Aplastic anaemia: continued cause for concern: annotation **1105**
Webber R G *see* Hudson I R B *et al*
Webber S, Wilkinson A R, Lindsell D, Hope P L, Dobson S R M and Isaacs D Neonatal pneumonia **207**
Weindling A M *see* Marlow N *et al*
  Thomas H M *et al*
Weir D C *see* Freeman W *et al*
Welbury J, Paynter A and Parkin J M Senior house officer posts in community paediatrics—an introduction to child health: personal paper **1009**
Welch R J *see* Wariyar U K *et al*
Weller P H Management of asthma: a consensus statement: correspondence **468**

see also Williams J *et al*
West M *see* Jones C *et al*
Wharton B A *see* Cross J H *et al*
Wheeldon J *see* Miller P F W *et al*
    Shaw N J *et al*
Wheeler K and Chessells J M UKALL X—an effective treatment for stage III mediastinal non-Hodgkin's lymphoma **252**
Whitaker H *see* Wailoo M P *et al*
White M P and Houston A B Pulmonary hypertension in bronchopulmonary dysplasia: correspondence **1378**
Whitehead J E *see* Freeman W *et al*
Whitehead R G *see* Waterston A J R *et al*
Whitelaw A Treatment of sepsis with IgG in very low birthweight infants: annotation **347** *fn*
Whitmore K and Bax M C O Checking the health of school entrants: personal practice **320**
Whittle M J *see* Swinhoe D J *et al*
Wight D G D *see* Sullivan P B *et al*
Wilkin T J *see* Voss L D *et al*
Wilkinson A R *see* Webber S *et al*
Wilkinson M J and Fagan D G Postmortem demonstration of intrapulmonary arteriovenous shunting **435**
    see also Barlow J *et al*
Willems C Daman- *see* Daman-Willems C
Williams A F *see* Aylett S E *et al*
Williams D *see* Pinkerton C R *et al*
Williams D M *see* Collins J E *et al*
Williams J, Macdonald A, Weller P H, Fields J and Pandov H Two enteric coated microspheres in cystic fibrosis **594**
Williams L H P and Bodden S J Early diet in preterm babies and developmental status in infancy: correspondence **914**
Williams S M, Taylor B J, Ford R P K and Nelson E A S Growth velocity before sudden infant death **1315**
Williamson J B, Galasko C S B and Robinson M J Outcome after acute osteomyelitis in preterm infants **1060** *fn*
Williamson S *see* Walker J M *et al*
Willoughby M L N *see* Minutillo C *et al*
Willshaw H *see* Muir K R *et al*
Willshaw H E *see* Roberts-Harry J *et al*
Wilson D C and Redmond A O B An unusual cause of thoracic mass **991**
Wilson D I, Appleton R E, Coulthard M G, Lee R E J, Wren C and Bain H H Fetal and infantile hypertension caused by unilateral renal arterial disease **881**
Wilson J A Health for all children: controversy—reviews of a book **142**
Wilson J M and Darby C R Perforated duodenal ulcer: an unusual complication of gastroenteritis **990**
Wilson L M K *see* Hawkins M M *et al*
Wilson N M and Silverman M Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home **407**
    see also Salmon B *et al*
Wilson-Storey D, Scobie W G and Mcgenity K G Microbiological studies of the enterocolitis of Hirschsprung's disease **1338**
Winchester B Prenatal diagnosis of enzyme defects: current topic **59** *fn*
Windebank K P The cytokines are coming: current topic **1283**
Winiarski J Platelet antigens in varicella associated thrombocytopenia **137**
Winrow A P and Supramaniam G Benign intracranial hypertension after ciprofloxacin administration **1165**
Wong H N *see* Lam B C C *et al*
Wong T W *see* Fung K P *et al*
Wong W *see* Fok T F *et al*
Wood P J *see* Walker J M *et al*
Wood S and Mccormick B Use of hearing aids in infancy: annotation **919**
Woods K L *see* Fenton A C *et al*
    Hodges S *et al*
Woolley H *see* Stein A *et al*
Wootton C *see* Pinkerton C R *et al*
Wootton S *see* Ahmed F *et al*
Working group of European Society of Paediatric Gastroenterology and Nutrition Revised criteria for diagnosis of coeliac disease: special report **909**
Wormald P J *see* Bass D H *et al*
Worthington B S *see* Elias-Jones A C *et al*
Wraith J E and Alani S M Carpal tunnel syndrome in the mucopolysaccharidoses and related disorders **962**
Wren C *see* Sreeram N and Wren C
    Wilson D I *et al*
Wright M *see* Sundaresan M *et al*
Wright S *see* Selikowitz M *et al*
Wynne J M *see* Hobbs C J and Wynne J M
Wyse R K H *see* Blake K D *et al*

Yap P L *see* Hague R A *et al*
    Mok J Y Q and Yap P L
Yap P L *see* Mok J Y Q and Yap P L
Yeomans E *see* Mclelland J *et al*
Yeung C K, Fu K H, Yuen K Y, Ng W F, Tsang T M, Branicki F J and Saing H *Helicobacter pylori* and associated duodenal ulcer **1212**
Yeung C Y *see* Lam B C C *et al*
Yin J A *see* Sung R Y T *et al*
Young M C and Hughes I A Dexamethasone treatment for congenital and adrenal hyperplasia **312**
    Response to treatment of congenital adrenal hyperplasia in infancy **441**
Yu V Y H *see* Sennhauser F H *et al*
Yudkin P L *see* Ahmed M L *et al*
Yuen K Y *see* Yeung C K *et al*
Yuksel B, Greenough A and Maconochie I Effective bronchodilator treatment by a simple spacer device for wheezy premature infants **782**

Zachello F *see* da Dalt L *et al*
Zaide J *see* Appleton R E *et al*
Zetterstrom R *see* Bier D M *et al*
Zucchini S *see* Cacciari E *et al*

Archives of Disease in Childhood 1990; 65: 1398–1405

VOLUME 65 · SUBJECT INDEX

Abdominal
  pain, recurrent, abnormal small bowel permeability and duodenitis, **1311**
  wall defects, antenatal diagnosis, missed opportunity, **687** *fn*
Acrodynia (pink disease): forty years ago, **1182**
Actinomycosis causing thoracic mass, **991**
Adolescents with severe intellectual handicap, survey, **1133**
Adrenal function in asthma, **838**
Aerosol
  amount reaching lungs, **401**
  therapy in the newborn: report of a workshop, **906**
AIDS and haemophilia, **1301**
Air leaks and vasopressin release, **1259**
Airway
  function in infants with vascular rings, preoperative and postoperative assessment, **171**
  obstruction, acute, increased plasma concentrations of prostaglandin metabolite: correspondence, **559**
Alfentanil pharmacokinetics, preterm infants, **349** *fn*
Allergic bronchopulmonary aspergillosis and cystic fibrosis, **507**
Alpha$_1$ antitrypsin deficiency, severe hypertension after liver transplantation, **1217**
Alpha fetoprotein, low serum as marker for diaphragmatic hernia: correspondence, **912**
Amniotic fluid insulin concentration as predictor of obesity, **1050** *fn*
Anaemia
  discovery at child health clinics, **892**
  risk factors in milk intake patterns, **428**; correspondence, **1184**
  preterm infants, red cell volume and cardiac output, **672** *fn*
Anal masturbation and nocturnal faecal soiling, **1367**
Aneurysms of the vein of Galen: correspondence, **337**

ANNOTATIONS
    Antibiotic treatment of suspected neonatal meningitis, **1** *fn*
    Aplastic anaemia: continued cause for concern, **1105**
    Atrial natriuretic factor: the heart as an endocrine organ, **1293**
    Audit—where do we go from here? **1107**
    Cerebral ultrasound and neurological impairment: telling the future, **469**
    Cold comfort for the catarrhal child, **1295**
    Craniosynostosis and the paediatrician, **568**
    Diagnosis and management of subglottic stenosis after neonatal ventilation, **1103**
    Do chesty children become chesty adults? **161**
    The genetics of deafness, **1196**
    Genomic imprinting, **1013** *fn*
    Head retraction and respiratory disorders in infancy, **567**
    Hearing screening in children—state of the art(s), **1193**
    Impairment, disability, and handicap, **819**
    Incidence and prevalence, **471**
    Management of infantile gastroenteritis, **917**
    Management of threadworm infestation during pregnancy, **399**
    Maternal employment, **565**
    Neonatal infections with coagulase negative staphylococci, **1015** *fn*
    New insights into the haemolytic uraemic syndromes, **713**
    Pathogenesis and management of aspergillosis in cystic fibrosis, **397**
    Phenobarbitone and febrile convulsions, **921**
    Postviral fatigue syndrome, **1198**
    Proper use of growth hormone, **70**
    Respiratory problems and cystic adenomatoid malformation of lung, **649** *fn*
    Rubella reinfection, **820**
    Somatic gene therapy for genetic disease, **72**
    Sore throats, **249**
    Surgery for gastro-oesophageal reflux, **1291**
    Terminology in community child health—an urgent need for consensus, **817**
    Transcutaneous carbon dioxide monitoring, **345** *fn*
    Treatment of sepsis with IgG in very low birthweight infants, **347** *fn*
    Use of hearing aids in infancy, **919**
Anti-*Escherichia coli* antibody, and immunoglubulin in lower respiratory tract secretions, less than 1500 g birthweight, **48** *fn*
Antibiotic treatment of suspected neonatal meningitis: annotation, **1** *fn*: correspondence, **810**
Anticonvulsant
  monitoring, rapid, in epilepsy clinic, **264**
  treatment after first fit, do children need?: Archivist, **1277**
Antidiuretic hormone, excessive secretion in infections with respiratory syncytial virus, **1237**
Antiemetic, 5-HT$_3$ antagonist ondansetron, in cancer treatment, **822**
Antimicrobial treatment for urinary tract infections: current topic, **327**
Antiviral and antibacterial lipids in human milk and infant formula feeds, **861**
Anorexia nervosa complicating inflammatory bowel disease, **298**
Aortopexy, role in management of primary tracheomalacia and tracheobronchomalacia, **438**
Aplastic anaemia, continued cause for concern: annotation, **1105**
  see also Anaemia
Arachnodactyly, contractural, with mitral regurgitation and iridodonesis, **317**; correspondence, **1012**
Arterial hypoxaemia, severe, and intrapulmonary shunting with recurrent cyanotic episodes, sudden death mechanism, **953**
Arteriovenous
  haemodiafiltration, continuous, for hypernatraemia correction, **628**
  malformations in vein of Galen: correspondence, **559**
Artificial
  food colours, effect on childhood behaviour, **74**
  surfactant (ALEC), premature babies treated with, follow up, **667** *fn*
Ascites, fetal, unusual presentation of Niemann-Pick disease type C: correspondence, **335**
Aspergillosis in cystic fibrosis, pathogenesis and management: annotation, **397**: correspondence, **1288**
Asphyxia, birth, acute renal failure after, **1021** *fn*
Aspirin use and Reye's syndrome, incidence trends, **826**
Asthma
  acute, episodic, intermittent high dose inhaled steroids, preschool children, **407**
  adrenal function, **838**
  bronchial, and acid reflux into distal and proximal oesophagus, **1255**
  deaths survey, Northern region, 1970–85, **163**
  management, consensus statement: correspondence, **468**
  prevalence, changes: correspondence, **646**
    increasing in rural adolescent population, New Zealand, 1975–89, **1319**
  questionnaire to measure perceived symptoms and disability, **779**
  school teachers knowledge, **622**
  self management plans: correspondence, **333**
Asthmatics, ventilated, long term outcome, **1324**
Atopic eczema
  and herpes simplex infections: correspondence, **333**
  hyponatraemia, and hypoalbuminaemia, **231**
Atrial natriuretic factor
  the heart as an endocrine organ: annotation, **1293**
  in hydrops fetalis caused by Rh isoimmunisation, **683** *fn*
Atrioventricular septal defect, complete, natural and modified history, 17 year study, **964**
Atropine, endotracheal and intravenous administration compared, **449**
Audit *see* Medical audit
Auditing community screening for undescended testes, **888**
Azathioprine treatment, hypertension after renal transplantation, **275**

Bacterial
  meningitis changes, **495**
  reservoirs in cystic fibrosis, **175**
Behaviour, childhood, effect of artificial food colours, **74**
Behavioural states, normal mature human fetuses, **39** *fn*
3β-hydroxy-Δ5-C$_{27}$-steroid dehydrogenase deficiency causing chronic liver disease, chenodeoxycholic acid in treatment, **1121**
Bilateral sensorineural hearing loss in children, prevalence of otitis media with effusion, **757**
Bilirubin binding to albumin, effect of indomethacin, **690** *fn*
Billard. Charles-Michel, (1800–1832), pioneer of neonatal medicine: perinatal lessons from the past, **711** *fn*
Birth
  natural, and Charles White (1728–1813): perinatal lessons from the past, **395** *fn*
  weight at full term and Ramadan, Asian Moslem pregnant women, Birmingham, **1053** *fn*
  less than 750 g, peak inspiratory pressure requirements, **1045** *fn*
  ratio and outcome, preterm infants, **30** *fn*
  specific trends in cerebral palsy, **602**
  very low, appropriate for gestational age, increases in pulsatile weight, **373** *fn*
    infants, cerebral palsy, **201**
    sepsis treated with IgG: annotation, **347** *fn*
Blood pressure, and cerebral blood flow velocity, on line measurement, neonates, new method, **11** *fn*
Body mass indices, properties and clinical implications, **516**
Bone
  mineral depletion, preterm infants, spontaneous resolution, **1038** *fn*
  mineralisation in twin to twin transfusion syndrome, **705** *fn*
Boric acid bottles or Dipslides for home collection of urine specimens, **286**

Breast
  feeding, decline, **369** *fn*
    duration and caesarean section, Brazil, **632**
  milk, human, lymphocytes bearing T cell receptor $\gamma\delta$, **1274**
Breath hydrogen excretion in infants with colic: correspondence, **248**
Breathing and hiccups, human fetuses, **1072** *fn*
British Paediatric Surveillance Unit: report, **807**
Bronchial asthma and acid reflux into distal and proximal oesophagus, **1255**
Bronchiectasis, ciliary aplasia, and hydrocephalus, **543**
Bronchiolitis, acute, latent sensitisation to respiratory syncytial virus during, and lung function after recovery, **946**
Bronchodilator treatment by simple spacer device for wheezy premature infants, **782**
Bronchopulmonary dysplasia
  dexamethasone treatment, catabolic state: correspondence, **560**
  early diagnosis, prophylaxis, and treatment: personal practice, **1082** *fn*
  new look at management: personal practice, **1089** *fn*
  severe, pulmonary circulation changes, **739**; correspondence, **1378**
  then and now: current topic, **1076** *fn*

Caesarean section and breast feeding duration, Brazil, **632**
Caffey's syndrome: forty years ago, **1164**
Calcium
  phosphate, and magnesium, renal excretion and intact parathyroid measurement, **1208**
  and phosphorus solubility in neonatal intravenous feeding solutions, **352** *fn*
Callosal hypoplasia in non-ketotic hyperglycinaemia, sonographic and pathological features, **670** *fn*
Cancer, childhood
  cure at what cost?: current topic, **638**
  late deaths after treatment, **1356**
  palliative care, home, hospital, or hospice: personal practice, **641**: correspondence, **1378**
  treatment, 5-HT$_3$ antagonist ondansetron as antiemetic, **822**
Capillary haemangioma presenting as lung pseudocyst, **1162**
Carbamazepine
  acute liver failure induced by, **315**
  slow release, in treatment of poorly controlled seizures, **930**
^{13}Carbon dioxide breath test to assess intraluminal lipolysis, **574**
Carbon dioxide monitoring, transcutaneous: annotation, **345** *fn*
Cardiac
  failure, neonatal, acquired transient protein C deficiency: correspondence, **158**
  output, and red cell volume, anaemic preterm infants, **672** *fn*
    reproducibility of measurements, Doppler ultrasound, newborn infants **15** *fn*
  tumours, fetal and neonatal, presenting with tuberous sclerosis, **377** *fn*
Cardiopulmonary bypass for resection of low tracheal haemangioma, **630**
Cardiothoracic ratio, prenatal measurement, in evaluation of heart disease, **20** *fn*
Career counselling and performance appraisal for senior house officers: medical education, **796**
Carpal tunnel syndrome in mucopolysaccharidoses and related disorders, **962**
Catarrhal child, cold comfort: annotation, **1295**
Central nervous system vasculitis after chickenpox, cause or coincidence? **1245**
Cerebral
  artery Doppler measurements, reproducibility: short report, **700** *fn*
  blood flow velocity and blood pressure, on line measurement, neonates, new method, **11** *fn*
  palsy, birthweight specific trends, **602**
    very low birthweight infants, **201**
    why we must plan for survival, **1329**
  ultrasound and neurological impairment, telling the future: annotation, **469**
CHARGE association, multidisciplinary management of patients, **217**
Charles White (1728–1813) and natural birth: perinatal lessons from the past, **395** *fn*
Chenodeoxycholic acid, in treatment of 3β-hydroxy-Δ5-C$_{27}$-steroid dehydrogenase deficiency causing chronic liver disease, **1121**
Chesty children, link with adult chest illnesses: annotation, **161**
Chickenpox, central nervous system vasculitis after, cause or coincidence? **1245**
Child health clinics, discovering anaemia, **892**
Child health, *Health for all children* (Hall, editor), 1989: controversy, **141**: correspondence, **812**
Childhood cancer *see* Cancer, childhood
Childhood morbidity 1947–9: forty years ago, **1182**
Children's services in new NHS, a struggle for survival?: current problems, **635**; correspondence, **1183**
Chlamydia trachomatis in infants, prospective study: correspondence, **336**
Chlamydial conjunctivitis, neonatal, diagnosis, **894**
Cholestasis, neonatal, presenting with Dubin-Johnson syndrome, **898**
Chromosomal abnormalities, and growth hormone deficiency: correspondence, **334**; **1183**
Chronic granulomatous disease, prognosis, **942**
Chylothorax, with generalised lymphangiomatosis : correspondence, **334**
Chymotrypsin, faecal levels in pancreatic exocrine function, **178**
Cilia, neonatal, ultrastructure, **708** *fn*
Ciliary aplasia, hydrocephalus, and bronchiectasis, **543**
Ciprofloxacin administration, benign intracranial hypertension after, **1165**
Circulatory adaptation, postnatal, healthy term and preterm neonates, **24** *fn*
Circumcision again: Archivist, **1181**
Cleft palate, submucous, in differential diagnosis of feeding difficulties, **182**
Coagulase negative staphylococci, neonatal infections: annotation, **1015** *fn*
Coeliac disease
  forty years ago, **609**
  following normal small bowel biopsy, **1137**
  revised criteria for diagnosis: special report, **909**
  timing for intestinal biopsy: correspondence, **810**
Cold comfort for the catarrhal child: annotation, **1295**
Colic, breath hydrogen excretion in infants with: correspondence, **248**
Colitis caused by food allergy in infants, **132**
Community
  child health, research: correspondence, **158**
    terminology, urgent need for consensus: annotation, **817**; correspondence, **1287**
  paediatrics, senior house officer posts, introduction to child health: personal paper, **1009**
Congenital adrenal hyperplasia
  dexamethasone treatment, **312**
  in infancy, response to treatment, **441**
  monitoring treatment: correspondence, **333**
Conjunctivitis, chlamydial, neonatal, diagnosis, **894**
Constipation associated with perianal appearances, **1231**
Continuous positive airway pressure in 1914, Dr von Reuss: perinatal lessons from the past, **68** *fn*
Coronary heart disease, risk factors in schoolboys and adult mortality rates, **78**
Corticosteroids in primary tuberculosis with bronchial obstruction, **1222**
Cot death and sleep position: current topic, **462**
Cranial ultrasonography, lateral ventricles area measured, preterm infants, reference range, **1029** *fn*; association with outcome, **1033** *fn*
Craniosynostosis and the paediatrician: annotation, **568**
Creon and Pancrease compared in cystic fibrosis, **594**
Crohn's disease
  growth after gut resection, **760**
  of the lung, **1270**
Cryptosporidiosis
  and acute leukaemia, **236**: correspondence, **813**
  intestinal, symptoms and transmission, **445**
Current Research Themes: Archivist, **1192**

CURRENT TOPICS
  Antimicrobial treatment for urinary tract infections, **327**
  Bronchopulmonary dysplasia: then and now, **1076** *fn*
  Childhood cancer; cure at what cost? **638**
  Choice of sleeping position for infants: possible association with cot death, **462**
  The cytokines are coming, **1283**
  Diagnosis and management of fetal growth retardation **390** *fn*
  Evaluating screening tests and screening programmes **792**
  Lung function testing in infancy, **548**
  Monitoring and sudden infant death syndrome: an update, **238**
  Paediatric medical audit, **1170**
  Prenatal diagnosis of enzyme defects, **59** *fn*
  Reflux vomiting, **996**
  Renal transplantation, **143**
  Retinal haemorrhages, **1369**
  The Royal Aberdeen Children's Hospital: 'Hospital of the year 1989', **900**
Cyanotic episodes, recurrent, with severe arterial hypoxaemia and intrapulmonary shunting, sudden death mechanism, **953**
Cyclophosphamide in nephrotic syndrome, eight and 12 week courses, **1147**
Cyclosporin treatment, hypertension after renal transplantation, **275**
Cystic adenomatoid malformation of lung, and respiratory problems: annotation, **649** *fn*
Cystic fibrosis
  and allergic bronchopulmonary aspergillosis, **507**
  and aspergillosis, pathogenesis and management: annotation, **397**; correspondence, **1288**
  bacterial reservoirs, **175**
  excessive faecal losses of vitamin A (retinol), **589**
  fluorescein dilaurate test of exocrine pancreatic function, **788**
  and haemophilus infection, **255**
  high dose pancreatic enzymes, **311**
  newborn screening, effects on reported maternal behaviour, **1240**
  nutrition: correspondence, **646**
  pathology mimicking distal intestinal obstruction syndrome, **540**

  personal practice, **152**
  and Pseudo-Bartter's syndrome, **786**
  Pseudomonas aeruginosa, and selective decontamination, **1365**
    serum IgA antibodies against, **259**
  Pseudomonas cepacia, new pathogen, **874**
  small intestinal permeability and orocaecal transit time, **585**
  and steatorrhoea, clinical monitoring, **99**: correspondence, **913**
  two enteric coated microspheres, **594**
Cytokines are coming, function, definition and future: current topic, **1283**

D-dimers, increased concentrations, newborn infants, **383** *fn*
D-lactic acidosis in short bowel syndrome, dietary management, **229**
Deafness
  genetics: annotation, **1196**
  sensorineural, screening by health visitors, **841**
  see also Hearing
Deaths
  preventable unexpected infant, categories, **535**
  late, after treatment for childhood cancer, **1356**
Dermatological treatment, salicylate poisoning: correspondence, **335**
Developmental
  deficiency syndrome, new, carbohydrate deficient serum transferrin, **107**
  status in infancy, and early diet in preterm babies: correspondence, **914**
Dexamethasone
  and infection, preterm babies, controlled study, **54** *fn*: correspondence, **812**
  treatment of bronchopulmonary dysplasia, catabolic state: correspondence, **560**
  for congenital adrenal hyperplasia, **312**
Diabetes
  insipidus continuous vasopressin replacement, **896**
    nephrogenic, and intracerebral calcification, **885**
  mellitus, dipyridamole effect on renal and platelet function, **93**
    early complications: correspondence, **247**
  control in children, general/paediatric clinics compared, **139**
Dialysis, peritoneal, access, neonates and infants, **44** *fn*: correspondence, **914**
Diaphragmatic hernia
  congenital, preoperative stabilisation, **1043** *fn*
    prostanoids impact in perioperative period, **994**
  low serum alpha fetoprotein as marker: correspondence, **912**
Diarrhoea
  chronic, *Helicobacter pylori*, Gambian children, **189**
  persistent, clinical efficacy and nutrient absorption with rice based diet, **294**
Diet, early, preterm babies, and developmental status in infancy: correspondence, **914**
Diphtheria, pertussis, and tetanus immunisation, first, rectal temperature of normal babies the night after, **1305**
Dipslides or boric acid bottles for home collection of urine specimens, **286**
Dipyridamole effect on renal and platelet function in diabetes mellitus, **93**
Disability, handicap, and impairment, terminology: annotation, **819**
DNA probes, intragenic, application in prenatal screening for retinoblastoma gene carriers, United Kingdom, **651** *fn*
Doppler measurements, cerebral artery, reproducibility, **700** *fn*
Down's syndrome
  with acute leukaemia, prognosis, **212**
  selenium supplementation to increase IgG$_2$ and IgG$_4$, **1353**
DPT *see* Diphtheria, pertussis, and tetanus immunisation
Drug reactions and food, wheezing, and eczema, preterm infants, **411**
Dubin-Johnson syndrome presenting with neonatal cholestasis, **898**
Ductus arteriosus, prostaglandin E$_2$ gel for cervical ripening and closure, newborn, **703** *fn*
Duodenal ulcer and *Helicobacter pylori*, **1212**
Duodenitis and abnormal small bowel permeability in recurrent abdominal pain, **1311**
Duplicate publication and related problems: editorial, **1289**
Dwarfism, Laron's, reduced sweating: correspondence, **1380**

Echo planar imaging and total body plethysmography, lung volume estimation in infants, **168**
Echocardiographic abnormalities in type IV mucopolysaccharidosis, **746**
Echodensities, intracerebral, transient neonatal, neurodevelopmental outcome, **27** *fn*
Eczema, and wheezing, food and drug reactions, preterm infants, **411**

EDITORIALS
  Duplicate publication and related problems, **1289**
  Style changes, **69**
  Writing economically, **251**
Egg and breast milk based nitrogen sources compared: correspondence, **336**
Encephalocele and meningomyelocele, systematic ventriculographic studies in infants born with, incidence and development of hydrocephalus: neonatology—then and now **246**
Encephalopathy, acute, virological investigations, India, **1227**
Endotoxin core glycolipid, serum immunoglobulins, establishment of normal concentrations, **768**: acute leukaemia and other cancers, **771**: correspondence, **1379**
Enterocolitis of Hirschsprung's disease, microbiological studies, **1338**
Enuresis, nocturnal
  determinants in homozygous sickle cell disease, **615**
  predicting treatment outcome, **1158**
  in sickle cell haemoglobinopathies, **290**
Enzyme defects, prenatal diagnosis: current topic, **59** *fn*
Epiglottitis, acute, children and adults, 1981–3, Sweden, **491**
Epilepsy
  clinic, rapid anticonvulsant monitoring, **264**
  do children need anticonvulsant treatment after first fit?: Archivist, **1277**
  treatment, people with multiple handicap: personal practice, **453**
European Journal of Paediatrics: sister journals—Europe, **1182**
Exchange transfusion, peripheral vessels use, **676** *fn*
Exercise ability after Mustard's operation, **865**
Exocrine pancreatic function, fluorescein dilaurate test, in cystic fibrosis, **788**

Faecal
  incontinence in normal children, paradoxical approach to management, **598**
  microflora, quantitative changes, preceding necrotising enterocolitis, premature neonates, **1057** *fn*
  soiling, nocturnal, and anal masturbation, **1367**
Failure to thrive, early childhood, recognising, **1263**
Fast ventilator rates
  circulatory effects, preterm infants, **662** *fn*
  preterm infants, circulatory effects, **662** *fn*
Febrile convulsions
  effect of fever on recurrence: correspondence, **333**
  and phenobarbitone: annotation, **921**
Feeding
  difficulties, submucous cleft palate in differential diagnosis, **182**
  and growth problems after oesophageal atresia repair, **84**
  solutions, intravenous *see* Intravenous feeding solutions
Fenfluramine in Prader-Willi syndrome, double blind, placebo controlled trial, **112**
Fetal growth retardation, diagnosis and management: current topic, **390** *fn*
Fetofetal transfusion syndrome, application of neonatal criteria in utero, **657** *fn*
Fetuses, human, hiccups and breathing, **1072** *fn*
Fluid shift from vascular compartment immediately after birth: neonatology—then and now, **331**
Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis, **788**
Fontanelle, anatomy and development, **386** *fn*
Food
  allergy, causing colitis in infants, **132**
  colours, artificial, effect on childhood behaviour, **74**
  and drug reactions, wheezing, and eczema, preterm infants, **411**
  for the premature brain: Archivist, **1265**
Foreign bodies, inhalation, long term follow up after, **619**
Fragile X mental retardation: correspondence, **335**
Fructose malabsorption, isolated, first year of life, **227**

Gastro-oesophageal reflux
  into distal and proximal oesophagus and bronchial asthma, **1255**
  pH monitoring, diagnostic accuracy: correspondence, **560**
  surgery: annotation, **1291**
Gastroenteritis
  and admission to hospital, **579**
  childhood, management, **939**
  forty years ago, **526**
  infantile, acute, under 6 months old, **936**
    management: annotation, **917**
  perforated duodenal ulcer as unusual complication, **990**
Genetic disease, somatic gene therapy: annotation, **72**
Genome, human, prospect for paediatrics: regular review, **457**
Genomic imprinting: annotation, **1013** *fn*
Giardia lamblia infestation: forty years ago, **767**
Glucose polymer regimens and hypernatraemia, **627**; correspondence, **1185**
Gonadal maturation assessment by spermaturia evaluation, **1205**
Growth
  after gut resection for Crohn's disease, **760**
  delay, final height, untreated, **1109**
  failure secondary to moyamoya syndrome, **232**; correspondence, **1012**
  and feeding problems after oesophageal atresia repair, **84**
  haemophilic boys after HIV infection, **115**
  hormone, proper use: annotation, **70**
    deficiency in children with chromosomal abnormalities: correspondence, **334**; **1183**
      urinary growth hormone excretion as screening test, **89**; correspondence, **811**
    and oxandrolone compared in growth and puberty delay, **448**

- urinary excretion, increase in puberty, **1203**
  - as screening test for growth hormone deficiency, **89**; correspondence, **811**
- parent-specific evaluation: correspondence, **647**
- and puberty delay, oxandrolone compared in growth hormone, **448**
- retardation, fetal, diagnosis and management: current topic, **390** *fn*
- screening, routine, and health visitors height measurements, **1345**
- and tubewell water, iron content, rural Bangladesh, **224**

Growth velocity before sudden infant death, **1315**

Gut blood flow velocities, newborn, effects of patent ductus arteriosus and parenteral indomethacin, **1067** *fn*

Haemangioma, low trachea, cardiopulmonary bypass for resection, **630**

Haemolytic uraemic syndromes
- in the British Isles 1985–1988, association with Verocytotoxin producing *Escherichia coli*. Part 1; clinical and epidemiological aspects, **716** Part 2: microbiological aspects, **722**
- new insights into: annotation, **713**
- and single kidney, renal functional reserve compared, **729**

Haemophagocytic syndrome, virus associated, and intravenous immunoglobulin, **1275**

Haemophilic
- boys, growth after HIV infection, **115**
- patients cohort and HIV-1 infection, **1301**

Haemophilus infection in cystic fibrosis, **255**

Haemophilus influenzae infections in siblings, need for prophylaxis, **489**

Handicap
- impairment, and disability, terminology: annotation, **819**
- multiple, treatment of epilepsy: personal practice, **453**

Handicapped children, teaching junior staff about caring: medical education, **903**

Harvey, Dr William (1578–1657): physician, obstetrician, and fetal physiologist: perinatal lessons from the past, **1098** *fn*

Head
- injured children, rehabilitation: personal practice, **553**
  - how community paediatricians can help: personal practice, **1286**
- retraction and respiratory disorders in infancy: annotation, **567**

Health, children's in schools: correspondence, **559**

Hearing
- aids in infancy: annotation, **919**
- impairment, parental suspicion and identification, **846**
- loss, early identification, screening and surveillance methods, **479**; correspondence, **1183**
- loss, screening infants: correspondence, **158**
- screening, children, state of the art(s): annotation, **1193**
- *see also* Deafness

Heart disease, prenatal measurement of cardiothoracic ratio in evaluation, **20** *fn*

Height
- final, boys with untreated constitutional delay in growth and puberty, **1109**
- measurement, health visitors measurements, and routine growth screening, **1345**
  - reliability, (Wessex Growth Study) **1340**
- and sleep habits, ages 5 to 11, **119**

Helicobacter pylori: regular review, **1278**
- and associated duodenal ulcer, **1212**
- in chronic diarrhoea and malnutrition, Gambian children, **189**
- and protein losing enteropathy: correspondence, **332**

Hepatic encephalopathy, acute, and nephroblastoma, **542**

Hepatitis B vaccination, intradermal, in thalassaemia, **527**

Hereditary syndrome, systemic, new, with carbohydrate deficient serum transferrin, **107**

Herpes simplex infections in atopic eczema: correspondence, **333**

HHV6 infection, acute, roseola infantum and other syndromes associated with, **1297**

Hiccups and breathing, human fetuses, **1072** *fn*

High frequency positive pressure ventilation in preterm infants, circulatory effects, **662** *fn*

Hirschsprung's disease, enterocolitis, microbiological studies, **1338**

Histiocytosis, Langerhans cell, case for conservative treatment, **301**

HIV infection
- growth in haemophilic boys after, **115**
- in haemophilic patients, **1301**
- and intravenous immunoglobulin: correspondence, **247**

'Hospital of the year 1989', Royal Aberdeen Children's Hospital: current topic, **900**

5-HT$_3$ antagonist ondansetron, effective antiemetic in cancer treatment, **822**

Human
- herpesvirus type 6 infection *see* HHV6
- immunodeficiency virus *see* HIV

Hydrocephalus
- bronchiectasis, and ciliary aplasia, **543**
- incidence and development, systematic ventriculographic studies in infants born with meningomyelocele and encephalocele: neonatology—then and now **246**

Hydrogen excretion, breath, in infants with colic: correspondence, **248**

Hydrops fetalis, atrial natriuretic factor, caused by Rh isoimmunisation, **683** *fn*

Hyperactive behaviour and artificial food colours, **74**

Hypercalcaemia, indomethacin responsive, associated with renal sarcoma, **1168**

Hyperinsulinaemic hypoglycaemia, small for dates babies, **1118**

Hypernatraemia
- correction with continuous arteriovenous haemodiafiltration, **628**
- and glucose polymer regimens: short report, **627**; correspondence, **1185**

Hypertension
- benign intracranial, after ciprofloxacin administration, **1165**
- essential, red cell membrane sodium transport, possible genetic role in identifying risk, **1154**
- fetal and infantile, caused by unilateral renal arterial disease, **881**
- after renal transplantation treated with cyclosporin and azathioprine, **275**
- severe, after liver transplantation in alpha$_1$ antitrypsin deficiency, **1217**

Hypoalbuminaemia, atopic eczema, and hyponatraemia, **231**

Hyponatraemia, hypoalbuminaemia, and atopic eczema, **231**

Hypoparathyroidism, short stature, and mental retardation, a new syndrome, **1113**

Hypophosphataemia, X linked, treatment, height gain, and nephrocalcinosis, **1125**

Hypophosphatasia with myopathy, **130**

Hypospadias, 5 alpha-reductase deficiency without, **1166**

Hypothalamo-pituitary area disorders, endocrine and morphological factor, MRI study, **1199**

Hypothyroidism, primary, thyroxine treatment, reappraisal, **1129**

Iced water treatment for supraventricular tachycardia in infants, **127**

Idiopathic thrombocytopenic purpura, chronic disease predictors, **502**

Ifosfamide, nephrotoxicity after, **752**

Illuminance of neonatal units, **679** *fn*

Immunisation state and its documentation in hospital, **763**

Immunity, previous maternal, congenital rubella after, **545**

Immunoglobulin
- A antibodies, serum, against *Pseudomonas aeruginosa* in cystic fibrosis, **259**
- and anti-*Escherichia coli* antibody in lower respiratory tract secretions, less than 1500 g birthweight, **48** *fn*

Immunoglobulin G, treatment of sepsis, very low birthweight: annotation, **347** *fn*
- intravenous, in HIV infection: correspondence, **247**
  - in virus associated haemophagocytic syndrome, **1275**
- serum, to endotoxin core glycolipid, establishment of normal concentrations, **768**; acute leukaemia and other cancers, **771**; correspondence, **1379**

Impairment, disability, and handicap, terminology: annotation, **819**

Incidence and prevalence, definitions: annotation, **471**

Indomethacin
- effect on binding of bilirubin to albumin, **690** *fn*
- parenteral, and patent ductus arteriosus effects on gut blood flow velocities, newborn, **1067** *fn*
- and the premature brain: Archivist, **1254**
- responsive hypercalcaemia associated with renal sarcoma, **1168**

Infantile
- cortical hyperostosis: forty years ago, **1164**
- gastroenteritis *see* Gastroenteritis, infantile

Inflammatory bowel disease, anorexia nervosa complicating, **298**

Inspiratory flow rate influence on effect of Turbuhaler, **308**

Insulin
- amniotic fluid, concentration as predictor of obesity, **1050** *fn*
- dependent diabetes mellitus, human isophane or lente insulin, double blind crossover trial, **1334**

Intellectual handicap, severe, survey of adolescents, **1133**

Intermittent positive pressure ventilation in asthmatics, long term outcome, **1324**

Intestinal obstruction syndrome, distal, in cystic fibrosis, pathology mimicking, **540**

Intracerebral
- calcificatinonand nephrogenic diabetes insipidus, **885**
- flares, neonatal, neurodevelopmental outcome, **27** *fn*

Intrapulmonary
- arteriovenous shunting, postmortem demonstration, **435**
- shunting, and severe arterial hypoxaemia with recurrent cyanotic episodes, sudden death mechanism, **953**

Intravenous feeding solutions
- formulation, and acidbase state, preterm infant, **354** *fn*
- neonatal, calcium and phosphorus solubility, **352** *fn*

Intubation, diagnosis and management of subglottic stenosis after: annotation, **1103**

Intussusception
- chronic, presentation and investigation, **134**
- factors related to treatment, **871**

Iridodonesis and mitral regurgitation with contractural arachnodactyly, **317**; correspondence, **1012**

Iron
  deficiency, preschool children, **610**
  supplementation, preterm or low birthweight infant: correspondence, **559**
  in tubewell water and linear growth, rural Bangladesh, **224**
Ischaemic brain lesions diagnosed at birth, preterm infants, clinical events and developmental outcome, **1017** *fn*
Isophane, human, or lente insulin, insulin dependent diabetes mellitus, double blind crossover trial, **1334**

James Spence Medallist, 1990, Professor Leonard B Strang, **1101**

Kala-azar in Scottish child, **1269**
Kasabach-Merritt syndrome, treatment with intermittent pneumatic compression, **790**
Kawasaki disease, echocardiographic features, 91 cases, United Kingdom, **1142**
Kidney
  function, which routine test?: correspondence, **561**
  single, and haemolytic uraemic syndrome, renal functional reserve compared, **728**
Klippel-Trenauny, and Sturge-Weber syndromes with absence of inferior vena cava, **546**

Lacerations, minor, topical anaesthesia for repair, **1272**
Lactobacilli, faecal, factors influencing presence of, early infancy, **185**
Langerhans cell histiocytosis, case for conservative treatment, **301**
Laron's dwarfism, reduced sweating: correspondence, **1380**
Late walking, marker of morbidity? **486**; correspondence, **1183**
Lateral ventricles area measured on cranial ultrasonography, preterm infants, reference range, **1029** *fn*; association with outcome, **1033** *fn*
Learning difficulties, severe, survey of adolescents, **1133**
Lente insulin or human isophane, insulin dependent diabetes mellitus, double blind crossover trial **1334**
Leukaemia, acute
  and cryptosporidiosis, **236**; correspondence, **813**
  with Down's syndrome, prognosis, **212**
    lymphoblastic, decline in head growth and cognitive impairment in survivors, **530**
    neurotoxicity, comparison of oral and intramuscular methotrexate and two doses of radiation, **416**
    serum immunoglobulins: correspondence, **1379**
  and other cancers, serum immunoglobulins to endotoxin core glycolipid, **771**; correspondence, **1379**
Lichen sclerosus and sexual abuse: correspondence, **335**; correspondence, **1184**
Life
  saving intervention in neonatal period, dilemmas and decisions: personal paper, **557**
  support withdrawal, babies, deceptive signals: personal view, **1096** *fn*
  threatening illness and hospice care: correspondence, **468**
Light, reaction to, and pupillary diameter, preterm neonates, **35** *fn*
Lighting of neonatal units, **679** *fn*
Lignocaine, adrenaline and cocaine, topical anaesthesia for minor laceration repair, **1272**
Linear growth, early neonatal period, **707** *fn*
Lipids, antiviral and antibacterial in human milk and infant formula feeds, **861**
Lipolysis, intraluminal, assessment using $^{13}CO_2$ breath test, **574**
Liver
  disease, chronic, chenodeoxycholic acid in 3β-hydroxy-$\Delta 5$-C_{27}-steroid dehydrogenase deficiency, **1121**
  failure, acute, induced by carbamazepine, **315**
  transplantation in alpha$_1$ antitrypsin deficiency, severe hypertension after, **1217**
Low tracheal haemangioma, cardiopulmonary bypass for resection, **630**
Lung
  and Crohn's disease, **1270**
  function, effects of overweight, **512**
    and respiratory sequelae after whooping cough in infancy, **569**
    testing in infancy: current topic, **548**
  pseudocyst, capillary haemangioma presenting as, **1162**
  volume estimation in infants by echo planar imaging and total body plethysmography, **168**
Lymphangiomatosis, generalised, with chylothorax: correspondence, **334**
Lymphocytes bearing T cell receptor $\gamma\delta$ in human breast milk, **1274**

Magnetic resonance imaging in neurological disorders, **922**
Malnutrition, *Helicobacter pylori*, Gambian children, **189**
Marfan's syndrome, contractural arachnodactyly versus: correspondence, **1012**
Markers of serious illness, infants under 6 months old presenting to children's hospital, **750**
Marrow aspiration from small infants: correspondence, **813**
Maternal
  behaviour, effects of newborn screening of cystic fibrosis, **1240**
  employment: annotation, **565**
  rubella reinfection: annotation, **820**
Mechanical ventilation and respiratory syncytial virus infection: correspondence, **332**
Medical audit
  paediatric: current topic, **1170**
  where do we go from here?: annotation, **1107**
Medical examinations, selective, for school entrants, the way forward: personal view, **1177**
Meetings, **159**
Membranes, prolonged and premature rupture, and chronic respiratory morbidity, **878**
Meningitis
  bacterial, changes, **495**
  neonatal, suspected, antibiotic treatment: annotation, **1** *fn*: correspondence, **810**
Meningomyelocele and encephalocele, systematic ventriculographic studies in infants born with, incidence and development of hydrocephalus: neonatology—then and now **246**
Mental retardation, hypoparathyroidism, and short stature, a new syndrome, **1113**
Methotrexate and radiation in acute lymphoblastic leukaemia, **416**
Microcytosis in preschool children, **610**
Migraine, management: personal practice, **1174**
Milk
  human and formula, antibacterial and antiviral lipids, **861**
  intake and anaemia, **428**: correspondence, **1184**
  taste: correspondence, **647**
Mitral
  obstruction, isolated, with neonatal pneumomediastinum, **56** *fn*
  regurgitation and iridodonesis with contractural arachnodactyly, **317**: correspondence, **1012**
Monitoring and suddent infant death syndrome, an update: current topic, **238**: correspondence, **913**
Mortality, postneonatal, international trends, **607**
Mosaic trisomy 16, live newborn infant, **388** *fn*
Mosaicism, XO/XY, in phenotypic males, **891**
Moyamoya syndrome, growth failure secondary to, **232**; correspondence, **1012**
Mucopolysaccharidoses
  and related disorders, and carpal tunnel syndrome, **962**
  type IV, echocardiographic abnormalities, **746**
Mustard's operation, exercise ability after, **865**
Myalgic encephalomyelitis *see* Postviral fatigue syndrome
Myopathy with hypophosphatasia, **130**

National Health Service, new, children's services, struggle for survival?: current problems, **635**; correspondence, **1183**
Necrotising enterocolitis, quantitative changes in faecal microflora preceding, premature neonates, **1057** *fn*
Neonatal units, illuminance, **679** *fn*
Neonates, studies: forty years ago, **767**
Nephroblastoma presenting with acute hepatic encephalopathy, **542**
Nephrocalcinosis, in X linked hypophosphataemia, **1125**
Nephrogenic diabetes insipidus and intracerebral calcification, **885**
Nephrosis, prednisolone pharmacokinetics, **196**
Nephrotic syndrome
  congenital, spontaenous resolution, neonate: short report, **992**
  eight and 12 week courses of cyclophosphamide, **1147**
Nephrotoxicity after ifosfamide, **732**
Neuroblastoma and Wilms' tumour, relative occurrence, ethnic subgroups, West Midlands Health Authority Region: correspondence, **1380**
Neurodevelopmental outcome, transient neonatal intracerebral echodensities, **27** *fn*
Neurological
  disorders, magnetic resonance imaging, **922**
  impairment, and cerebral ultrasound, telling the future: annotation, **469**
  manifestations of osteoid osteoma, **851**
Neurologically impaired infants, and early diet, prematurity: correspondence, **914**
Niemann-Pick disease type C, fetal ascites as unusual presentation: correspondence, **335**
Nights, disturbed, feeding and thermal environment, **499**
Nitrogen sources, egg and breast milk based compared: correspondence, **336**
Non-attendance in outpatient paediatric clinics, understanding, **192**; correspondence, **913**
Non-Hodgkin's lymphoma, mediastinal, UKALL X effective treatment for stage III, **252**
Non-ketotic hyperglycinaemia, callosal hypoplasia, sonographic and pathological features, **670** *fn*

Obesity, amniotic fluid insulin concentrations as predictor, **1050** *fn*
Obstruction, upper airway, acute, management in intensive care unit, district general hospital: personal practice, **241**
Oculokinetic perimetry for assessment of visual fields, **432**

Oesophageal
  atresia repair, growth and feeding problems after, **84**
  pH studies, 24 hour, infants, reproducibility, **1249**
Ondansetron, 5-HT_3 antagonist, effective antiemetic in cancer treatment, **822**
Optic nerve hypoplasia, associations and management, **103**
Orocaecal transit time and small intestinal permeability in cystic fibrosis, **585**
Osteoid osteoma, neurological manifestations, **851**
Osteomyelitis, acute, outcome after, preterm infants, **1060** *fn*
Otitis media with effusion, prevalence in children with bilateral sensorineural hearing loss, **757**
Outpatient paediatric clinics, non-attendance, understanding, **192**; correspondence, **913**
Overweight, effects on lung function, **512**
Oxandrolone and human growth hormone compared in growth and puberty delay, **448**
Ozone in medical gases: correspondence, **1185**

Paediatric training, examinations: medical education, **1004**
Palliative care for children with cancer, home, hospital, or hospice: personal practice, **641**; correspondence, **1378**
Pancrease and Creon compared in cystic fibrosis, **594**
Pancreatic
  enzymes, high dose, in cystic fibrosis, **311**
  exocrine function, ontogeny, **178**
Papaveretum infusion, continuous, for pain control in painful sickling crisis, **1151**
Paracetamol pharmacokinetics after cardiac surgery, **971**
Parathyroid hormone, intact serum, indices, and renal excretion of calcium, phosphate, and magnesium, **1208**
Parenteral
  nutrition solutions, two, neonates, clinical trial, **692** *fn*
  suspicion and identification of hearing impairment, **846**
Parkin, Michael, an international paediatrician: contemporary history, **802**
Patent ductus arteriosus and parenteral indomethacin effects on gut blood flow velocities, newborn, **1067** *fn*
Peak inspiratory pressure requirements, birthweight less than 750 g, **1045** *fn*
Pediatriia, sister journals, Soviet Union, **1011**
Percutaneous central venous catheters, neonatal, retention, and *Staphylococcus epidermidis*, **234**; correspondence, **915**
Perforated duodenal ulcer, unusual complication of gastroenteritis, **990**
Performance appraisal and career counselling for senior house officers: medical education, **796**
Perianal appearances associated with constipation, **1231**
Peripheral vessels, use for exchange transfusion, **676** *fn*
Peritoneal dialysis access, neonates and infants, **44** *fn*; correspondence, **914**
Periventricular leucomalacia, diagnosed at birth in preterm infants, clinical events and developmental outcome, **1017** *fn*

PERSONAL PRACTICE
  Bronchopulmonary dysplasia: early diagnosis, prophylaxis, and treatment, **1082** *fn*
  Bronchopulmonary dysplasia: a new look at management, **1089** *fn*
  Checking the health of school entrants, **320**
  Cystic fibrosis, **152**
  Development of a psychiatric liaison service, **1373**
  Head injury—how community paediatricians can help, **1286**
  Management of acute upper airway obstruction in an intensive care unit in a district general hospital, **241**
  Management of migraine, **1174**
  Paediatrician to a special school, **803**
  Palliative care for children with cancer—home, hospital, or hospice? **641**
  Psychological guidelines in the management of paediatric organ transplantation, **1000**
  Rehabilitation of head injured children, **553**
  Treatment of epilepsy in people with multiple handicap, **453**
Pertussis, pulmonary collapse: forty years ago, **526**
pH
  monitoring in gastro-oesophageal reflux, diagnostic accuracy: correspondence, **560**
  studies, oesophageal, 24 hour, infants, reproducibility, **1249**
Phaeochromocytoma, investigation and management of 10 cases, **269**
Phenobarbitone and febrile convulsions: annotation, **921**
Phenylketonuria, intelligence and quality of dietary treatment, **472**
Phosphorus and calcium solubility in neonatal intravenous feeding solutions, **352** *fn*
Pink disease (acrodynia): forty years ago, **1182**
Plasma
  shift, postnatal, in premature infants: neonatology—then and now, **331**
  volume changes in the newborn (1958/59): neonatology—then and now, **331**
Platelet antigens in varicella associated thrombocytopenia, **137**
Plethysmography, total body, and echo planar imaging, lung volume estimation in infants, **168**
Pneumatic compression, intermittent, treatment for Kasabach-Merritt syndrome, **790**
Pneumococcal prophylaxis after splenectomy, continued need, **1268**
Pneumocystis carinii pneumonia diagnosis from non-invasive sampling of respiratory secretions, **1364**
Pneumomediastinum, neonatal, with isolated mitral obstruction, **56** *fn*
Pneumonia, neonatal, incidence, aetiology and outcome, **207**
Postgraduate training for the next decade, Europe: medical education, **644**
Posthaemorrhagic ventricular dilatation, neonatal, early tapping, randomised trial, **3** *fn*
Postneonatal mortality, international trends, **607**
Postviral fatigue syndrome: annotation, **1198**
Potassium, maternofetal, absent gradient at term, **384** *fn*
Prader-Willi syndrome, and fenfluramine, double blind, placebo controlled trial, **112**
Prednisolone pharmacokinetics in nephrosis, **196**
Pregnancy, threadworm infestation during, management: annotation, **399**
Prenatal
  diagnosis, enzyme defects: current topic, **59** *fn*
  measurement, cardiothoracic ratio in evaluation of heart disease, **20** *fn*
Preschool children, microcytosis, iron deficiency, and thalassaemia, **610**
Pressure flow characteristics of spacer devices valves: correspondence, **159**
Prevalence and incidence, definitions: annotation, **471**
Probability, qualitative expressions, interpretation by parents, **520**: correspondence, **1379**
Prolactin, plasma, and clinical outcome, preterm infants, **977**
Prostaglandin
  E_2 gel for cervical ripening and closure of ductus arteriosus in newborn, **703** *fn*
  metabolite in acute airway obstruction, increased plasma concentrations: correspondence, **559**
Prostanoids impact, congenital diaphragmatic hernia in perioperative period, **994**
Protein
  C deficiency, acquired transient, in neonatal cardiac failure: correspondence, **158**
    transient, and neonatal purpura fulminans: correspondence, **561**
  losing enteropathy, and *Helicobacter pylori*: correspondence, **332**
Pseudo-Bartter's syndrome in cystic fibrosis, **786**
Pseudomonas aeruginosa
  cystic fibrosis, and selective decontamination, **1365**
  serum IgA antibodies against, **259**
Pseudomonas cepacia, new pathogen in cystic fibrosis, **874**
Psychiatric liaison service, development: personal practice, **1373**
Psychological characteristics, children with Shwachman syndrome, **1349**
Puberty
  delay, final height, untreated, **1109**
  urinary growth hormone excretion increase, **1203**
Publication in journals, duplication and related problems: editorial, **1289**
Pulmonary
  circulation changes in severe bronchopulmonary dysplasia, **739**; correspondence, **1378**
  collapse in pertussis: forty years ago, **526**
Pulse oximetry in measurement of transcutaneous oxygen saturation in sleeping infants, **524**
Pupillary diameter and reaction to light, preterm neonates, **35** *fn*
Purpura fulminans, neonatal, and transient protein C deficiency: correspondence, **561**

Qualitative expressions of probability, interpretation by parents, **520**; correspondence, **1379**

Radiation and methotrexate in acute lymphoblastic leukaemia, **416**
Ramadan and birthweight at full term, Asian Moslem pregnant women, Birmingham, **1053** *fn*
Recombinant human growth hormone treatment of short stature in renal disease, **856**
Rectal-skin temperature difference in septicaemic newborn infants, **380** *fn*
Red cell
  membrane sodium transport, possible genetic role and use in identifying essential hypertension risk, **1154**
  volume and cardiac output in anaemic preterm infants, **672** *fn*
Reductase, 5 alpha, deficiency without hypospadias, **1166**
Referees, **1376**
Reflux vomiting: current topic, **996**
Renal
  arterial disease, unilateral, causing fetal and infantile hypertension, **881**
  disease, short stature, treatment with recombinant human growth hormone, **856**
  failure, acute, after birth asphyxia, **1021** *fn*
  functional reserve compared in haemolytic uraemic syndrome and single kidney, **728**
  sarcoma associated with indomethacin responsive hypercalcaemia, **1168**
  size, ultrasound measurement, newborn infants, **361** *fn*
  solute load, preterm infants, **357** *fn*
  transplantation: current topic, **143**

    hypertension after, treated with cyclosporin and azathioprine, **275**
Respiratory
  disorders and head retraction in infancy: annotation, **567**
  distress syndrome, circulatory effects, fast ventilator rates, preterm infants, **662** *fn*
  morbidity, chronic, after prolonged and premature rupture of the membranes, **878**
  problems and cystic adenomatoid malformation of lung: annotation, **649** *fn*
  rate and illness severity, babies under 6 months old, **834**
  sequelae and lung function after whooping cough in infancy, **569**
  syncytial virus, and excessive secretion of antidiuretic hormone in infections, **1237**
    infection and mechanical ventilation: correspondence, **332**
    latent sensitisation, during acute bronchiolitis and lung function after recovery, **946**
  tract, immunoglobulin and anti-*Escherichia coli* antibody, less than 1500 g birthweight, **48** *fn*
Retinal haemorrhages: current topic, **1369**
Retinoblastoma
  gene carriers, intragenic DNA probes application in prenatal screening, United Kingdom, **651** *fn*
  increasing incidence: correspondence, **915**
Reye's syndrome, incidence, trends, and aspirin use, **826**
Rh
  haemolytic disease, continuing problem of management, **365** *fn*
  isoimmunisation causing atrial natriuretic factor in hydrops fetalis, **683** *fn*
Rice base diet, clinical efficacy and nutrient absorption in persistent diarrhoea, **294**
Roseola infantum and other syndromes associated with acute HHV6 infection, **1297**
Royal Aberdeen Children's Hospital, 'Hospital of the year 1989': current topic, **900**
Royal Free disease *see* Postviral fatigue syndrome
RNA probes for maternal rubella diagnosis: annotation, **820**
Rubella
  congenital, after previous maternal immunity, **545**
  reinfections: annotation, **820**

Salicylate poisoning in dermatological treatment: correspondence, **335**
School
  children's health: correspondence, **559**
  entrants, checking health of: personal practice, **310**
    selective medical examinations, the way forward: personal view, **1177**
  health service through parents' eyes: correspondence, **336**
    medical, five year, time for change, **225**; correspondence, **912**
  teacher's knowledge about asthma, **622**
Screening tests and screening programmes, evaluating: current topic, **792**
Seizures, poorly controlled, slow release carbamazepine in treatment, **930**
Selenium supplementation to increase IgG_2 and IgG_4 in Down's syndrome, **1353**
Self hypnotherapeutic treatment of habitual reflex vomiting, **626**
Senior house officers, performance appraisal and career counselling: medical education, **796**
Senior house officer posts, community paediatrics, introduction to child health: personal paper, **1009**
Sensorineural deafness, screening by health visitors, **841**
Sepsis, treatment with immunoglobulin G, very low birthweight: annotation, **347** *fn*
Septicaemic newborn infants, rectal-skin temperature difference, **380** *fn*
Serious illness markers, infants under 6 months old presenting to children's hospital, **750**
Sextuplets, preterm, five year outcome related to size at birth, **451**
Sexual abuse, and lichen sclerosus: correspondence, **335**; correspondence, **1184**
Sexually abused battered child, **423**
Short
  bowel syndrome, D-lactic acidosis, dietary management, **229**
  reports, writing economically: editorial, **251**
  stature, mental retardation, and hypoparathyroidism, a new syndrome, **1113**
    in renal disease, treatment with recombinant human growth hormone, **856**
  and sleep habits, **119**
Shwachman syndrome, psychological characteristics of children with, **1349**
Sialic acid storage disease, **314**
Sickle cell
  disease, homozygous, nocturnal enuresis determinants, **615**
  haemoglobinopathies, and nocturnal enuresis, **290**
Sickling crisis, painful, continuous papaveretum infusion for pain control, **1151**
Skin conductance and arousal, in newborn, **1063** *fn*
Sleep
  disturbed, feeding and thermal environment, **499**
  habits and height, ages 5 to 11, **119**
  induction and white noise, **135**
  position and cot death: current topic, **462**
Sleeping at home, thermographic imaging, 3 month-old infants, **1266**
Small
  bowel biopsy, normal, followed by coeliac disease, **1137**
    permeability, abnormal, and duodenitis in recurrent abdominal pain, **1311**
      and orocaecal transit time in cystic fibrosis, **585**
  for dates babies, and hyperinsulinaemic hypoglycaemia, **1118**
Sodium
  cromoglycate, amount reaching lungs by aerosol, **401**
    nebulised, in infancy, airway protection after deterioration, **404**
  transport, red cell membrane and essential hypertension, **1154**
Somatic gene therapy for genetic disease: annotation, **72**
Sore throats: annotation, **249**
Soviet Union, Pediatriia, sister journal, **1011**
Special school paediatrician: personal practice, **803**
Spermaturia evaluation, gonadal maturation assessment, **1205**
Splenectomy
  continued need for pneumococcal prophylaxis after, **1268**
  partial, in homozygous beta thalassaemia, **304**
Stabilisation, preoperative, congenital diaphragmatic hernia, **1043** *fn*
Staphylococci, coagulase negative, neonatal infections: annotation, **1015** *fn*
Staphylococcus epidermidis and retention of neonatal percutaneous central venous catheters, **234**; correspondence, **915**
Statistics, Annual Statistical Review, 1988, **147**
Steatorrhoea in cystic fibrosis, clinical monitoring, **99**; correspondence, **913**
Steroids, intermittent high dose inhaled, in acute episodic asthma in preschool children, **407**
Sturge-Weber and Klippel-Trenauny syndromes with absence of inferior vena cava, **546**
Style changes: editorial, **69**
Subglottic stenosis after neonatal ventilation, diagnosis and management: annotation, **1103**
Sudden
  death mechanism, recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting, **953**
  infant death syndrome, growth velocity before, **1315**
    incidence, ethnic differences, Birmingham, **830**
    and monitoring, an update, current topic, **238**: correspondence, **913**
    see also Sudden infant death syndrome
    and sufactant abnormality, primary or secondary phenomenon? **774**
Supraventricular tachycardia in infants, response to initial treatment, **127**
Surfactant abnormality and sudden infant death syndrome, primary or secondary phenomenon? **774**
Sweating, reduced, in Laron's dwarfism: correspondence, **1380**
Symptoms in 298 infants under 6 months old, seen at home, **280**

T cell receptor γδ, lymphocytes bearing, in human breast milk, **1274**
Tapping, early, in neonatal posthaemorrhagic ventricular dilatation, randomised trial, **3** *fn*
Teaching junior staff about caring for handicapped children: medical education, **903**
Temperature, body, factors influencing 3–4 month old infants at home during the day, **1308**
  rectal, of normal babies night after first diphtheria, pertussis, and tetanus immunisation **1305**
  rectal-skin, difference in septicaemic newborn infants, **380** *fn*
Terminology
  in community child health, urgent need for consensus: annotation, **817**: correspondence, **1287**
  impairment, disability, and handicap: annotation, **819**
Thalassaemia, beta homozygous, and partial splenectomy, **304**
  intradermal hepatitis B vaccination, **527**
  older, social integration, **984**
  preschool children, **610**
Thermographic imaging to study babies sleeping at home, **1266**
Thoracic mass, unusual cause—actinomycosis, **991**
Threadworm infestation during pregnancy, management: annotation, **399**
Thrombocytopenia, varicella associated, and platelet antigens, **137**
Thrush in infancy: forty years ago, **1164**
Thyroxine treatment in primary hypothyroidism, reappraisal, **1129**
Tonsillectomy: forty years ago, **767**
Topical anaesthesia for minor lacerations repair, **1272**
Tracheobronchomalacia, and primary tracheomalacia, role of aortopexy in management, **438**
Tracheomalacia, primary, and tracheobronchomalacia, role of aortopexy in management, **438**
Tracheostomy, review of 142 patients over 10 years, **123**
Training, paediatric, examinations: medical education, **1004**
Transcutaneous
  carbon dioxide monitoring: annotation, **345** *fn*
  oxygen saturation in sleeping infants, **524**
Transferrin, carbohydrate deficient serum, in new systemic hereditary syndrome, **107**
Transplantation, organ, paediatric, psychological guidelines in management: personal practice, **1000**

Trisomy 16, mosaic, live newborn infant, **388** *fn*
Trisomy 18, long term survival: Archivist, **1216**
Tuberculosis, primary, with bronchial obstruction, and corticosteroids, **1222**
Tuberous sclerosis presenting with fetal and neonatal cardiac tumours, **377** *fn*
Turbuhaler, influence of inspiratory flow rate on effect, **308**
Twin to twin transfusion syndrome, bone mineralisation: short report, **705** *fn*

UKALL X, effective treatment for stage III mediastinal non-Hodgkin's lymphoma, **252**
Ultrasound
  cerebral, and neurological impairment, telling the future: annotation, **469**
  cranial, lateral ventricles area measured, preterm infants, reference range, **1029** *fn*; association with outcome, **1033** *fn*
  measurement of renal size, newborn infants, **361** *fn*
Undescended testes, auditing community screening for, **888**
Unexpected infant deaths, preventable, categories, **535**
  see also Sudden infant death syndrome
Upper airway obstruction, acute, management in intensive care unit, district general hospital: personal practice, **241**
Urinary tract infections, antimicrobial treatment: current topic, **327**
Urine speciemens
  home collection, boric acid bottles or Dipslides, **286**
  24 hour, collecting from children: correspondence, **1184**

Varicella associated thrombocytopenia, and platelet antigens, **137**
Vascular
  compartment, fluid shift from, immediately after birth: neonatology—then and now, **331**
  rings, airway function in infants, preoperative and postoperative assessment, **171**
Vasculitis, central nervous system, after chickenpox, cause or coincidence? **1245**
Vasopression
  continuous replacement, in diabetes insipidus, **896**
  release and air leaks, **1259**
Vein of Galen aneurysms: correspondence, **337**
Ventilator dependency, United Kingdom, **1235**
Ventriculographic studies, systematic, in infants born with meningomyelocele and encephalocele, incidence and development of hydrocephalus: neonatology—then and now **246**
Verocytotoxin producing *Escherichia coli*, association with haemolytic uraemic syndromes in the British Isles 1985–1988. Part I: clinical and epidemiological aspects, **716**; Part 2: microbiological aspects, **722**; annotation, **713**
Virilisation, female preterm infants, **701** *fn*
Virus associated haemophagocytic syndrome and intravenous immunoglobulin, **1275**
Visceral leishmaniasis in Scottish child, **1269**
Visual fields, oculokinetic perimetry for assessment, **432**
Vitamin A (retinol), excessive faecal losses, in cystic fibrosis, **589**
Vomiting, reflex, habitual, self hypnotherapeutic treatment, **626**
Von Reuss, Dr, on continuous positive airway pressure in 1914: perinatal lessons from the past, **68** *fn*

Walking, late, marker of morbidity? 486; correspondence, **1183**
Weight, pulsatile, increases in very low birthweight, appropriate for gestational age, **373** *fn*
Wessex Growth Study, height measurement reliability, **1340**
Wheezing, and eczema, food and drug reactions, preterm infants, **411**
Wheezy premature infants, effective bronchodilator treatment by simple spacer device, **782**
White noise and sleep induction, **135**
Whooping cough in infancy, respiratory sequelae and lung function after, **569**
Williams syndrome, the iris in, **987**
Wilms' tumour
  and neuroblastoma, relative occurrence, ethnic subgroups, West Midland Health Authority Region: correspondence, **1380**
  relapsed, curability, **968**
Writing economically, short reports: editorial, **251**

XO/XY mosaicism in phenotypic males, **891**

ARCHIVES OF DISEASE IN CHILDHOOD

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VOLUME 65 · CONTENTS

No 1 JANUARY 1990

FETAL AND NEONATAL EDITION

Annotation

1 Antibiotic treatment of suspected neonatal meningitis *G Gandy, J Rennie*

Original articles

3 Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation *Ventriculomegaly Trial Group*
11 On line cerebral blood flow velocity and blood pressure measurement in neonates: a new method *A C Fenton, D H Evans, M I Levene*
15 Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound *I Hudson, A Houston, T Aitchison, et al*
20 Prenatal measurement of cardiothoracic ratio in evaluation of heart disease *D Paladini, S K Chita, L D Allan*
24 Postnatal circulatory adaptation in healthy term and preterm neonates *N J Evans, L N J Archer*
27 Neurodevelopmental outcome of transient neonatal intracerebral echodensities *R E Appleton, R E J Lee, E N Hey*
30 Birthweight ratio and outcome in preterm infants *R Morley, O G Brooke, T J Cole, et al*
35 Pupillary diameter and reaction to light in preterm neonates *J Robinson, A R Fielder*
39 Behavioural states in normal mature human fetuses *M Pillai, D James*
44 Access for peritoneal dialysis in neonates and infants *M A Lewis, I B Houston, R J Postlethwaite*
48 Immunoglobulin and anti-Escherichia coli antibody in lower respiratory tract secretions from infants weighing less than 1500 g at birth *F H Sennhauser, A Balloch, M J Shelton, et al*
54 Dexamethasone and infection in preterm babies: a controlled study *P C Ng, M A Thomson, P R F Dear*
56 Neonatal pneumomediastinum with isolated mitral obstruction *C L Case, P Oslizlok, D Fyfe, et al*

Current topic

59 Prenatal diagnosis of enzyme defects *B Winchester*

Perinatal lessons from the past

68 Dr von Reuss on continuous positive airway pressure in 1914 *P M Dunn*

No 1 JANUARY 1990

69 **Editorial**

Annotations

70 Proper use of growth hormone *R D G Milner*
72 Somatic gene therapy for genetic disease *C Kinnon, R J Levinsky*

Original articles

74 Effect of artificial food colours on childhood behaviour *I Pollock, J O Warner*
78 Association between risk factors for coronary heart disease in schoolboys and adult mortality rates in the same localities *W Freeman, D C Weir, J E Whitehead, et al*
84 Growth and feeding problems after repair of oesophageal atresia *J W L Puntis, D G Ritson, C E Holden, et al*
89 Urinary growth hormone excretion as a screening test for growth hormone deficiency *J M Walker, P J Wood, S Williamson, et al*
93 Absence of effect of dipyridamole on renal and platelet function in diabetes mellitus *D M Gibb, D Dunger, M Levin, et al*
99 Clinical monitoring of steatorrhoea in cystic fibrosis *M P Walters, J Kelleher, J Gilbert, et al*
103 Optic nerve hypoplasia: associations and management *J Roberts-Harry, S H Green, H E Willshaw*
107 Carbohydrate deficient serum transferrin in a new systemic hereditary syndrome *H Stibler, J Jaeken*
112 Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial *M Selikowitz, J Sunman, A Pendergast, et al*
115 Growth in haemophilic boys after HIV infection *K J Pasi, M A Collins, A K Ewer, et al*
119 Sleep habits and height at ages 5 to 11 *M C Gulliford, C E Price, R J Rona, et al*
123 Tracheostomy *N J Freezer, S W Beasley, C F Robertson*
127 Supraventricular tachycardia in infants: response to initial treatment *N Sreeram, C Wren*
130 Myopathy with hypophosphatasia *S S Seshia, G Derbyshire, J C Haworth, et al*
132 Colitis caused by food allergy in infants *S M Hill, P J Milla*
134 Chronic intussusception *A C Page, J F Price, J R Salisbury, et al*
135 White noise and sleep induction *J A D Spencer, D J Moran, A Lee, et al*
137 Platelet antigens in varicella associated thrombocytopenia *J Winiarski*
139 Is a specialist paediatric diabetic clinic better? *S Bloomfield, J W Farquhar*

Controversy— reviews of a book

141 Health for all children *M C O Bax, K Whitmore, J A Wilson, A Colver*

Current topic

143 Renal transplantation *R S Trompeter*

Review

147 Annual statistical review *P O D Pharoah, E D Alberman*

Personal practice

152 Cystic fibrosis *T J David*

158 **Letters to the editor**

159 **Meetings in 1990**

160 **Instructions to authors**

No 2 FEBRUARY 1990

Annotation

161 Do chesty children become chesty adults? *D P Strachan*

Original articles

163 Survey of asthma deaths in the Northern region, 1970–85 *H J Fletcher, S A Ibrahim, N Speight*
168 Estimation of lung volume in infants by echo planar imaging and total body plethysmography *B Chapman, C O'Callaghan, R Coxon, et al*
171 Airway function in infants with vascular rings: preoperative and postoperative assessment *A H Thomson, C S Beardsmore, R Firmin, et al*

175 Bacterial reservoirs in cystic fibrosis *C J Taylor, J McGaw, R Howden, et al*
178 Ontogeny of pancreatic exocrine function *S Kolacek, J W L Puntis, D R Lloyd, et al*
182 Submucous cleft palate in the differential diagnosis of feeding difficulties *A L H Moss, K Jones, R W Pigott*
185 Factors influencing the presence of faecal lactobacilli in early infancy *M A Hall, C B Cole, S L Smith, et al*
189 Helicobacter pylori in Gambian children with chronic diarrhoea and malnutrition *P B Sullivan, J E Thomas, D G D Wight, et al*
192 Understanding non-attendance in outpatient paediatric clinics *R Andrews, J D Morgan, D P Addy, et al*
196 Pharmacokinetics of prednisolone in children with nephrosis *P F W Miller, C J Bowmer, J Wheeldon, et al*
201 Cerebral palsy in very low birthweight infants *R W I Cooke*
207 Neonatal pneumonia *S Webber, A R Wilkinson, D Lindsell, et al*
212 Prognosis of Down's syndrome with acute leukaemia *G A Levitt, C A Stiller, J M Chessells*
217 Who's in CHARGE? Multidisciplinary management of patients with CHARGE association *K D Blake, I M Russell-Eggitt, D W Morgan, et al*
224 Iron in tubewell water and linear growth in rural Bangladesh *A Briend, B A Hoque, K M A Aziz*
225 The five year school medical—time for change *G C Smith, A Powell, K Reynolds, et al*
227 Isolated fructose malabsorption *J K H Wales, R A Primhak, J Rattenbury, et al*
229 Dietary management of D-lactic acidosis in short bowel syndrome *A J Mayne, D J Handy, M A Preece, et al*
231 Atopic eczema, hyponatraemia, and hypoalbuminaemia *H M Goodyear, J I Harper*
232 Growth failure secondary to moyamoya syndrome *C A MacKenzie, R D G Milner, U Bergvall, et al*
234 Staphylococcus epidermidis and retention of neonatal percutaneous central venous catheters *G Gladman, S Sinha, D G Sims, et al*
236 Cryptosporidiosis and acute leukaemia *A B M Foot, A Oakhill, M G Mott*

Current topic

238 Monitoring and sudden infant death syndrome: an update *Report from the Foundation for the Study of Infant Deaths and the British Paediatric Respiratory Group*

Personal practice

241 Management of acute upper airway obstruction in an intensive care unit in a district general hospital *G H Lear, S A McKenzie, H Boralessa*

246 **Neonatology—then and now** *C H M Walker*

247 **Letters to the editor**

No 3 MARCH 1990

Annotation

249 Sore throats *H Marcovitch*

251 **Editorial**

Original articles

252 UKALL X—an effective treatment for stage III mediastinal non-Hodgkin's lymphoma *K Wheeler, J M Chessells*
255 Haemophilus infection in cystic fibrosis *R J Rayner, E J Hiller, P Ispahani, et al*
259 Serum IgA antibodies against Pseudomonas aeruginosa in cystic fibrosis *M M Brett, A T M Ghoneim, J M Littlewood*
264 Rapid anticonvulsant monitoring in an epilepsy clinic *P N Houtman, S K Hall, A Green, et al*
269 Phaeochromocytoma—investigation and management of 10 cases *J E Deal, P S Sever, T M Barratt, et al*
275 Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine *N Gordjani, G Offner, P F Hoyer, et al*
280 Symptoms in 298 infants under 6 months old, seen at home *A J Thornton, C J Morley, P H Hewson, et al*
286 Home collection of urine specimens—boric acid bottles or Dipslides? *F E M Jewkes, D J McMaster, W A Napier, et al*
290 Nocturnal enuresis in sickle cell haemoglobinopathies *D R J Readett, J S Morris, G R Serjeant*
294 Persistent diarrhoea: clinical efficacy and nutrient absorption with a rice based diet *S K Roy, R Haider, M S Akbar, et al*
298 Anorexia nervosa complicating inflammatory bowel disease *P Mallett, S Murch*
  Commentary *B Lask*
301 Langerhans cell histiocytosis: the case for conservative treatment *J McLelland, V Broadbent, E Yeomans, et al*
304 Partial splenectomy in homozygous β thalassaemia *M de Montalembert, R Girot, Y Revillon, et al*
308 Influence of inspiratory flow rate upon the effect of a Turbuhaler *S Pedersen, O R Hansen, G Fuglsang*
311 High dose pancreatic enzymes in cystic fibrosis *P J Robinson, P D Sly*
312 Dexamethasone treatment for congenital adrenal hyperplasia *M C Young, I A Hughes*
314 Sialic acid storage disease *P D Cameron, V Dubowitz, G T N Besley, et al*
315 Acute liver failure induced by carbamazepine *N Hadžić, B Portmann, E T Davies, et al*
317 Contractural arachnodactyly with mitral regurgitation and iridodonesis *I C Huggon, J P Burke, J F Talbot*

Personal practice

320 Checking the health of school entrants *K Whitmore, M C O Bax*

Current topic

327 Antimicrobial treatment for urinary tract infections *K Verrier Jones*

331 **Neonatology—then and now** *C H M Walker*

332 **Letters to the editor**

338 **Spring books**

FETAL AND NEONATAL EDITION

No 4 APRIL 1990

Annotations

345 Transcutaneous carbon dioxide monitoring *J M Rennie*
347 Treatment of sepsis with IgG in very low birthweight infants *A Whitelaw*

Original articles

349 Alfentanil pharmacokinetics in preterm infants *N Marlow, A M Weindling, A Van Peer, et al*
352 Calcium and phosphorus solubility in neonatal intravenous feeding solutions *P MacMahon, P D Mayne, M Blair, et al*
354 Acid-base state of the preterm infant and the formulation of intravenous feeding solutions *P MacMahon, P D Mayne, M Blair, et al*

357 Renal solute load in preterm infants *M De Curtis, J Senterre, J Rigo*
361 Ultrasound measurement of renal size in newborn infants *J E S Scott, E W Hunter, R E J Lee, et al*
365 Rh haemolytic disease—continuing problem of management *D J Swinhoe, D H Gilmore, M B McNay, et al*
369 Decline in breast feeding *J L Emery, S Scholey, E M Taylor*
373 Pulsatile weight increase in very low birthweight babies appropriate for gestational age *L Greco, A Capasso, C De Fusco, et al*
377 Tuberous sclerosis presenting with fetal and neonatal cardiac tumours *G Wallace, H C Smith, G H Watson, et al*
380 Rectal-skin temperature difference in septicaemic newborn infants *J Messaritakis, D Anagnostakis, H Laskari, et al*
383 Increased concentrations of D-dimers in newborn infants *I R B Hudson, B E S Gibson, J Brownlie, et al*
384 Absent maternofetal potassium gradient at term *T Mohammed, M Maresh, C P Sibley, et al*
386 Anatomy and development of the fontanelle *M Sundaresan, M Wright, A B Price*
388 Mosaic trisomy 16 in a live newborn infant *N J Gilberston, J W Taylor, I Z Kovar*

Current topic

390 Diagnosis and management of fetal growth retardation *D James*

Perinatal lessons from the past

395 Charles White (1728–1813) and natural birth *P M Dunn*

No 4 APRIL 1990

Annotations

397 Pathogenesis and management of aspergillosis in cystic fibrosis *E J Hiller*
399 Management of threadworm infestation during pregnancy *F N Leach*

Original articles

401 How much aerosol reaches the lungs of wheezy infants and toddlers? *B Salmon, N M Wilson, M Silverman*
404 Nebulised sodium cromoglycate in infancy: airway protection after deterioration *C O'Callaghan, A D Milner, A Swarbrick*
407 Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home *N M Wilson, M Silverman*
411 Food and drug reactions, wheezing, and eczema in preterm infants *A Lucas, O G Brooke, T J Cole, et al*
416 Neurotoxicity in lymphoblastic leukaemia *J M Chessells, T C S Cox, B Kendall, et al*
423 The sexually abused battered child *C J Hobbs, J M Wynne*
428 Surveillance for anaemia: risk factors in patterns of milk intake *A F Mills*
432 Oculokinetic perimetry for the assessment of visual fields *B J Clark, C Timms, W A Franks*
435 Postmortem demonstration of intrapulmonary arteriovenous shunting *M J Wilkinson, D G Fagan*
438 Role of aortopexy in the management of primary tracheomalacia and tracheobronchomalacia *P S Malone, E M Kiely*
441 Response to treatment of congenital adrenal hyperplasia in infancy *M C Young, I A Hughes*
445 Symptoms and transmission of intestinal cryptosporidiosis *M Egger, D Mäusezahl, P Odermatt, et al*
448 Treatment of constitutional delay of growth and puberty with oxandrolone compared with growth hormone *A Buyukgebiz, P C Hindmarsh, C G D Brook*
449 Endotracheal compared with intravenous administration of atropine *R F Howard, R M Bingham*
451 Five year outcome of preterm sextuplets related to size at birth *N Marlow, A M Ellis, B J Roberts, et al*

Personal practice

453 Treatment of epilepsy in people with multiple handicap *H Foley*

Regular review

457 The human genome: a prospect for paediatrics *R M Gardiner*

Current topic

462 Choice of sleeping position for infants: possible association with cot death *A C Engelberts, G A de Jonge*

468 **Letters to the editor**

No 5 MAY 1990

Annotations

469 Cerebral ultrasound and neurological impairment: telling the future *M I Levene*
471 Incidence and prevalence *P O D Pharoah*

Original articles

472 Intelligence and quality of dietary treatment in phenylketonuria *I Smith, M G Beasley, A E Ades*
479 Early identification of hearing loss: screening and surveillance methods *P E Scanlon, J M Bamford*
  Commentary *B McCormick*
486 Is late walking a marker of morbidity? *A Johnson, O Goddard, H Ashurst*
489 Haemophilus influenzae infections in siblings: the need for prophylaxis *A Dale, S Court*
  Commentary *E R Moxon*
491 Acute epiglottitis in children and adults in Sweden 1981–3 *B Trollfors, O Nylén, K Strangert*
495 Changes in bacterial meningitis *P E Carter, S M Barclay, W H Galloway, et al*
499 Disturbed nights in 3–4 month old infants—the effects of feeding and thermal environment *M P Wailoo, S A Petersen, H Whittaker*
502 Idiopathic thrombocytopenic purpura: predictors of chronic disease *L G Robb, K Tiedeman*
507 Cystic fibrosis and allergic bronchopulmonary aspergillosis *E J Simmonds, J M Littlewood, E G V Evans*
512 Effects of overweight on lung function *K P Fung, S P Lau, O K W Chow, et al*
516 Properties and clinical implications of body mass indices *K P Fung, J Lee, S P Lau, et al*
520 How do parents of babies interpret qualitative expressions of probability? *N J Shaw, P R F Dear*
524 Transcutaneous oxygen saturation in sleeping infants: prone and supine *S Levene, S A McKenzie*
527 Intradermal hepatitis B vaccination in thalassaemia *S Leonardi, T Reggio, A Sciacca, et al*
530 Decline in head growth and cognitive impairment in survivors of acute lymphoblastic leukaemia *R E Appleton, K Farrell, J Zaide, et al*
535 Categories of preventable unexpected infant deaths *E M Taylor, J L Emery*
540 Pathology mimicking distal intestinal obstruction syndrome in cystic fibrosis *A M Dalzell, D P Heaf, H Carty*
542 Nephroblastoma presenting with acute hepatic encephalopathy *S Kinmond, R Carter, C H Skeoch, et al*
543 Hydrocephalus, bronchiectasis, and ciliary aplasia *M M De Santi, A Magni, E A Valletta, et al*
545 Congenital rubella after previous maternal immunity *B D Das, P Lakhani, J B Kurtz, et al*
546 Sturge-Weber and Klippel-Trenauny syndromes with absence of inferior vena cava *G Stewart, G Farmer*

Current topic

548 Lung function testing in infancy *A D Milner*

Personal practice

553 Rehabilitation of head injured children *D M B Hall, S L J Johnson, J Middleton*

Personal paper

557 Life saving intervention in the neonatal period: dilemmas and decisions *P M Dunn*

559 **Letters to the editor**

562 **Book reviews**

No 6 JUNE 1990

Annotations

565 Maternal employment *P J Graham*
567 Head retraction and respiratory disorders in infancy *P Chidiac, I S Alexander*
568 Craniosynostosis and the paediatrician *R Hayward*

Original articles

569 Respiratory sequelae and lung function after whooping cough in infancy *I Krantz, J Bjure, I Claesson, et al*
574 Non-invasive assessment of intraluminal lipolysis using a $^{13}CO_2$ breath test *M S Murphy, E J Eastham, R Nelson, et al*
579 Admission to hospital with gastroenteritis *S P Conway, R R Phillips, S Panday*
585 Small intestinal permeability and orocaecal transit time in cystic fibrosis *A M Dalzell, N S Freestone, D Billington, et al*
589 Excessive faecal losses of vitamin A (retinol) in cystic fibrosis *F Ahmed, J Ellis, J Murphy, et al*
594 Two enteric coated microspheres in cystic fibrosis *J Williams, A MacDonald, P H Weller, et al*
598 Paradoxical approach to the management of faecal incontinence in normal children *B Knights, S K Pandey*
Commentary *K Asen*
602 Birthweight specific trends in cerebral palsy *P O D Pharoah, T Cooke, R W I Cooke, et al*
607 International trends in postneonatal mortality *E A Mitchell*
610 Microcytosis, iron deficiency, and thalassaemia in preschool children *A Earley, H B Valman, D Altman, et al*
615 Determinants of nocturnal enuresis in homozygous sickle cell disease *D R J Readett, J Morris, G R Serjeant*
619 Long term follow up after inhalation of foreign bodies *H Davies, I Gordon, D J Matthew, et al*
622 What do school teachers know about asthma? *M Bevis, B Taylor*
626 Self hypnotherapeutic treatment of habitual reflex vomiting *B S Sokel, S P Devane, A Bentovim, et al*
627 Glucose polymer regimens and hypernatraemia *I G Verber, M Bain*
628 Correction of hypernatraemia with continuous arteriovenous haemodiafiltration *G D Moss, R J Primavesi, M E McGraw, et al*
630 Cardiopulmonary bypass for resection of low tracheal haemangioma *R Franks, M Rothera*
632 Caesarean section and duration of breast feeding among Brazilians *C G Victora, S R A Huttly, F C Barros, et al*

Current problems

635 Children's services in the new NHS—a struggle for survival? *W J Appleyard*

Current topic

638 Childhood cancer: cure at what cost? *P H Morris-Jones, A W Craft*

Personal practice

641 Palliative care for children with cancer—home, hospital, or hospice? *A Goldman, S Beardsmore, J Hunt*

Medical education

644 Postgraduate training in Europe for the next decade *Organising Committee for the Workshop on Postgraduate Paediatric Training in Europe*

646 **Letters to the editor**

648 **Instructions to authors**

No 7 JULY 1990

FETAL AND NEONATAL EDITION

Annotation

649 Respiratory problems and cystic adenomatoid malformation of lung *J Walker, R E Cudmore*

Original articles

651 Application of intragenic DNA probes in prenatal screening for retinoblastoma gene carriers in the United Kingdom *Z O Onadim, C D Mitchell, P C Rutland, et al*
657 Fetofetal transfusion syndrome: do the neonatal criteria apply in utero? *N M Fisk, A Borrell, C Hubinont, et al*
662 Circulatory effects of fast ventilator rates in preterm infants *A C Fenton, D J Field, K L Woods, et al*
667 Follow up of premature babies treated with artificial surfactant (ALEC) *C J Morley, R Morley*
670 Sonographic and pathological features of callosal hypoplasia in non-ketotic hyperglycinaemia *U K Wariyar, R J Welch, D W A Milligan, et al*
672 Red cell volume and cardiac output in anaemic preterm infants *I Hudson, A Cooke, B Holland, et al*
676 Use of peripheral vessels for exchange transfusion *T K Fok, L Y So, K W Leung, et al*
679 Illuminance of neonatal units *J Robinson, M J Moseley, A R Fielder*
683 Atrial natriuretic factor in hydrops fetalis caused by Rh isoimmunisation *F R Moya, P A T Grannum, L Riddick, et al*
687 Antenatal diagnosis of abdominal wall defects: a missed opportunity? *J P Roberts, D M Burge*
690 Effect of indomethacin on binding of bilirubin to albumin *B C C Lam, H N Wong, C Y Yeung*
692 A clinical trial of two parenteral nutrition solutions in neonates *N McIntosh, V Mitchell*
700 Reproducibility of cerebral artery Doppler measurements *B Moorthy, P R Colditz, K N Ives, et al*
701 Virilisation of female preterm infants *P C Midgley, D Azzopardi, N Oates, et al*
703 Topical prostaglandin E_2 gel for cervical ripening and closure of the ductus arteriosus in the newborn *R Y T Sung, J A Yin, E P L Loong, et al*
705 Paradoxical bone mineralisation in the twin to twin transfusion syndrome *N J Bishop, F J King, P Ward, et al*
707 Linear growth in the neonatal period *N J Bishop, F J King, A Lucas*
708 Neonatal cilia: ultrastructure *J Barlow, M J Wilkinson, C O'Callaghan*

Perinatal lessons from the past

711 Charles-Michel Billard (1800–1832): pioneer of neonatal medicine *P M Dunn*

No 7 JULY 1990

Annotation

713 New insights into the haemolytic uraemic syndrome *D V Milford, C M Taylor*

Original articles

716 Haemolytic uraemic syndromes in the British Isles 1985–8: association with Verocytotoxin producing Escherichia coli. Part 1: clinical and epidemiological aspects *D V Milford, C M Taylor, B Guttridge, et al*
722 Haemolytic uraemic syndromes in the British Isles 1985–8: association with Verocytotoxin producing Escherichia coli. Part 2: microbiological aspects *H Kleanthous, H R Smith, S M Scotland, et al*
728 Renal functional reserve compared in haemolytic uraemic syndrome and single kidney *E M Perelstein, B G Grunfeld, R B Simsolo, et al*
732 Nephrotoxicity after ifosfamide *R Skinner, A J D Pearson, L Price, et al*
739 Changes in pulmonary circulation in severe bronchopulmonary dysplasia *A Bush, C M Busst, W B Knight, et al*
746 Echocardiographic abnormalities in type IV mucopolysaccharidosis *R M John, D Hunter, R H Swanton*
750 Markers of serious illness in infants under 6 months old presenting to a children's hospital *P H Hewson, S M Humphries, D M Roberton, et al*
757 Prevalence of otitis media with effusion in children with bilateral sensorineural hearing loss *V K Das*
760 Growth after gut resection for Crohn's disease *B I McLain, P M Davidson, K B Stokes, et al*
763 Immunisation state and its documentation in hospital patients *M J Ferson*
768 Serum immunoglobulins to endotoxin core glycolipid: establishment of normal concentrations *S K Jackson, J Parton, G Shortland, et al*
771 Serum immunoglobulins to endotoxin core glycoplipid: acute leukaemia and other cancers *S K Jackson, J Parton, G Shortland, et al*
774 Surfactant abnormality and the sudden infant death syndrome—a primary or secondary phenomenon? *D James, P J Berry, P Fleming, et al*
779 Questionnaire to measure perceived symptoms and disability in asthma *T P Usherwood, A Scrimgeour, J H Barber*
782 Effective bronchodilator treatment by a simple spacer device for wheezy premature infants *B Yuksel, A Greenough, I Maconochie*
786 Pseudo-Bartter's syndrome in cystic fibrosis *J D Kennedy, R Dinwiddie, C Daman-Willems, et al*
788 Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis *A M Dalzell, D P Heaf*
790 The Kasabach-Merritt syndrome: treatment with intermittent pneumatic compression *S E Aylett, A F Williams, D H Brown, et al*

Current topic

792 Evaluating screening tests and screening programmes *A E Ades*

Medical education

796 Performance appraisal and career counselling for senior house officers *M P Ward Platt, J M Parkin*

Contemporary history

802 Michael Parkin—an international paediatrician *A J R Waterston, A Aynsley-Green, L T Weaver, et al*

Personal practice

803 Paediatrician to a special school *S Lewis*

British Paediatric Association

807 Report from the British Paediatric Surveillance Unit *S M Hall, M Glickman*
810 **Letters to the editor**
814 **Book reviews**

No 8 AUGUST 1990

Annotations

817 Terminology in community child health—an urgent need for consensus *David H Stone*
819 Impairment, disability, and handicap *P O D Pharoah*
820 Rubella reinfection *Elizabeth Miller*

Original articles

822 5-HT_3 antagonist ondansetron—an effective outpatient antiemetic in cancer treatment *C R Pinkerton, D Williams, C Wootton, et al*
826 Trends in the incidence of Reye's syndrome and the use of aspirin *J D H Porter, P H Robinson, J F T Glasgow, et al*
830 Ethnic differences in incidence of sudden death syndrome *D Kyle, R Sunderland, M Stonehouse, et al*
834 Respiratory rate and severity of illness in babies under 6 months old *C J Morley, A J Thornton, M A Fowler, et al*
838 Adrenal function in asthma *K Priftis, A D Milner, E Conway, et al*
841 Screening for sensorineural deafness by health visitors *Ann Johnson, Hazel Ashurst*
846 Parental suspicion and identification of hearing impairment *P M Watkin, M Baldwin, S Laoide*
851 Neurological manifestations of osteoid osteoma *L Kiers, L K Shield, W G Cole*
856 Treatment of short stature in renal disease with recombinant human growth hormone *Lesley Rees, Susan P A Rigden, Geraldine Ward, et al*
861 Antiviral and antibacterial lipids in human milk and infant formula feeds *Charles E Isaacs, Sudha Kashyap, William C Heird, et al*
865 Exercise ability after Mustard's operation *J J Bowyer, C M Busst, J A Till, et al*
871 Intussusception: factors related to treatment *J A M Reijnen, C Festen, R P van Roosmalen*
874 Pseudomonas cepacia: a new pathogen in patients with cystic fibrosis *E J Simmonds, S P Conway, A T M Ghoneim, et al*
878 Chronic respiratory morbidity after prolonged and premature rupture of the membranes *P J Thompson, Anne Greenough, K Nicolaides*
881 Fetal and infantile hypertension caused by unilateral renal arterial disease *D I Wilson, R E Appleton, M G Coulthard, et al*
885 Nephrogenic diabetes insipidus and intracerebral calcification *O Schofer, R Beetz, K Kruse, et al*
888 Auditing community screening for undescended testes *R C Tamhne, S N Jarvis, A J R Waterston*
891 XO/XY mosaicism in phenotypic males *K Walker, A J Gunn, P D Gluckman*
892 Discovering anaemia at child health clinics *E Marder, A Nicoll, L Polnay, et al*
894 Diagnosis of neonatal chlamydial conjunctivitis *G Phillips, J S Forsyth, I A Harper*
896 Continuous vasopressin replacement in diabetes insipidus *Charles Ralston, Warwick Butt*
898 Dubin-Johnson syndrome presenting with neonatal cholestasis *Chi-Chang Shieh, Mei-Hwei Chang, Chi-Long Chen*

Current topic

900 The Royal Aberdeen Children's Hospital: 'Hospital of the year 1989' *G Russell*

Medical education

903 Teaching junior staff about caring for handicapped children *L Rosenbloom, N Marlow*

Report of a workshop

906 Aerosol therapy in the newborn *M Silverman*

Special report

909 Revised criteria for diagnosis of coeliac disease *Report of the Working Group of The European Society of Paediatric Gastroenterology and Nutrition*
912 **Letters to the editor**
916 **Book reviews**

No 9 SEPTEMBER 1990

Annotations

917 Management of infantile gastroenteritis *J A Walker-Smith*
919 Use of hearing aids in infancy *Sally Wood, Barry McCormick*
921 Phenobarbitone and febrile convulsions *D P Addy*

Original articles

922 Magnetic resonance imaging in neurological disorders *Alun C Elias-Jones, Timothy Jaspan, David H Mellor, et al*
930 Slow release carbamazepine in treatment of poorly controlled seizures *S W Ryan, I Forsythe, R Hartley, et al*
936 Acute gastroenteritis in infants under 6 months old *R Fox, C L S Leen, E M Dunbar, et al*
939 Management of gastroenteritis *H R Jenkins, B M Ansari*
942 Prognosis of chronic granulomatous disease *A Finn, N Hadžić, G Morgan, et al*
946 Latent sensitisation to respiratory syncytial virus during acute bronchiolitis and lung function after recovery *S J Caswell, A H Thomson, S P Ashmore, et al*
953 Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death *D P Southall, M P Samuels, D G Talbert*
962 Carpal tunnel syndrome in the mucopolysaccharidoses and related disorders *J E Wraith, S M Alani*
964 Natural and modified history of complete atrioventricular septal defect—a 17 year study *P Frontera-Izquierdo, G Cabezuelo-Huerta*
968 How curable is relapsed Wilms' tumour? *J J Groot-Loonen, C R Pinkerton, P H Morris-Jones, et al*
971 Pharmacokinetics of paracetamol after cardiac surgery *C S Hopkins, S Underhill, P D Booker*
977 Plasma prolactin and clinical outcome in preterm infants *A Lucas, B A Baker, T J Cole*
984 Social integration of the older thalassaemic patient *C Politis, A Di Palma, M Fisfis, et al*
987 The iris in Williams syndrome *G Holmström, G Almond, K Temple, et al*
990 Perforated duodenal ulcer: an unusual complication of gastroenteritis *Jane M Wilson, Christopher R Darby*
991 An unusual cause of thoracic mass *D C Wilson, A O B Redmond*
992 Spontaneous resolution of congenital nephrotic syndrome in a neonate *C R Banton, B Thalayasingam, M G Coulthard*
994 Congenital diaphragmatic hernia: impact of prostanoids in the perioperative period *A P Bos, D Tibboel, F W J Hazebroek, et al*

Current topic

996 Reflux vomiting *P J Milla*

Personal practice

1000 Psychological guidelines in the management of paediatric organ transplantation *Roger Bradford, Laura Tomlinson*

Medical education

1004 Examinations in paediatric training *Graham S Clayden*

Personal paper

1009 Senior house officer posts in community paediatrics—an introduction to child health *Jan Welbury, Arthur Paynter, J M Parkin*
1011 **Sister journals—the Soviet Union** *R H D Boyd*
1012 **Letters to the editor**

FETAL AND NEONATAL EDITION

No 10 OCTOBER 1990

Annotations

1013 Genomic imprinting *Judith G Hall*
1015 Neonatal infections with coagulase negative staphylococci *M R Millar, N Todd, P MacKay*

Original articles

1017 Ischaemic brain lesions diagnosed at birth in preterm infants: clinical events and developmental outcome *S K Sinha, S W D' Souza, E Rivlin, et al*
1021 Prediction of acute renal failure after birth asphyxia *D S Roberts, G B Haycock, R N Dalton, et al*
1029 Area of lateral ventricles measured on cranial ultrasonography in preterm infants: reference range *Elie Saliba, Philippe Bertrand, Francis Gold, et al*
1033 Area of lateral ventricles measured on cranial ultrasonography in preterm infants: association with outcome *Elie Saliba, Philippe Bertrand, Francis Gold, et al*
1038 Spontaneous resolution of bone mineral depletion in preterm infants *P J Congdon, A Horsman, S W Ryan, et al*
1043 Preoperative stabilisation in congenital diaphragmatic hernia *L K R Shanbhogue, P K H Tam, G Ninan, et al*
1045 Peak inspiratory pressure requirements in infants born weighing less than 750 g *Keith D Foote, Alexander H Hoon Jr, Sam Sheps, et al*
1050 Amniotic fluid insulin concentration as a predictor of obesity *Boyd E Metzger, Bernard L Silverman, Norbert Freinkel, et al*
1053 Ramadan and birth weight at full term in Asian Moslem pregnant women in Birmingham *J H Cross, J Eminson, B A Wharton*
1057 Quantitative changes in faecal microflora preceding necrotising enterocolitis in premature neonates *C Hoy, M R Millar, P MacKay, et al*
1060 Outcome after acute osteomyelitis in preterm infants *J B Williamson, C S B Galasko, M J Robinson*
1063 Skin conductance and arousal in the newborn *G Gladman, M L Chiswick*
1067 Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin *R C Coombs, M E I Morgan, G M Durbin, et al*
1072 Hiccups and breathing in human fetuses *Mary Pillai, David James*

Current topic

1076 Bronchopulmonary dysplasia: then and now *William H Northway Jr*

Personal practices

1082 Bronchopulmonary dysplasia: early diagnosis, prophylaxis, and treatment *Anne Greenough*
1089 Bronchopulmonary dysplasia: a new look at management *D P Southall, M P Samuels*

Personal view

1096 Withdrawal of life support in babies: deceptive signals *M L Chiswick*

Perinatal lessons from the past

1098 Dr William Harvey (1578–1657): physician, obstetrician, and fetal physiologist *P M Dunn*

No 10 OCTOBER 1990

1101 **James Spence Medallist 1990**

Annotations

1103 Diagnosis and management of subglottic stenosis after neonatal ventilation *M S C Morrissey, C M Bailey*
1105 Aplastic anaemia: continued cause for concern *David K H Webb*
1107 Audit—where do we go from here? *R I Ross Russell, P J Helms*

Original articles

1109 Final height in boys with untreated constitutional delay in growth and puberty *E C Crowne, S M Shalet, W H B Wallace, et al*
1113 Short stature, mental retardation, and hypoparathyroidism: a new syndrome *R J Richardson, J M W Kirk*
1118 Hyperinsulinaemic hypoglycaemia in small for dates babies *J E Collins, J V Leonard, D Teale, et al*
1121 Treatment of chronic liver disease caused by 3β-hydroxy-$\Delta 5$-C_{27}-steroid dehydrogenase deficiency with chenodeoxycholic acid *H Ichimiya, H Nazer, T Gunasekaran, et al*
1125 X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis *G S Reusz, P F Hoyer, M Lucas, et al*
1129 Reappraisal of thyroxine treatment in primary hypothyroidism *S Hodges, B P O'Malley, B N Northover, et al*
1133 Survey of adolescents with severe intellectual handicap *J C Asthana, S Sinha, J S Haslam, et al*
1137 Normal small bowel biopsy followed by coeliac disease *M Mäki, K Holm, S Koskimies, et al*
1142 Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom *A Suzuki, E J Tizard, V Gooch, et al*
1147 Eight and 12 week courses of cyclophosphamide in nephrotic syndrome *N Ueda, K Kuno, S Ito*
1151 Continuous papaveretum infusion for the control of pain in painful sickling crisis *Patricia C E Sartori, Graham J Gordon, Philip J Darbyshire*
1154 Red cell membrane sodium transport: possible genetic role and use in identifying patients at risk of essential hypertension *J E Deal, V Shah, G Goodenough, et al*
1158 Predicting treatment outcome in nocturnal enuresis *J B Devlin, C O'Cathain*
1162 Capillary haemangioma presenting as a lung pseudocyst *J J Bowyer, M Sheppard*
1165 Benign intracranial hypertension after ciprofloxacin administration *A P Winrow, G Supramaniam*
1166 5 α-Reductase deficiency without hypospadias *W K Ng, N F Taylor, I A Hughes, et al*
1168 Indomethacin responsive hypercalcaemia associated with a renal sarcoma *J Gibbs, M J Dillon, S Lang, et al*

Current topic

1170 Paediatric medical audit *R Primavesi, R MacFaul*

Personal practice

1174 Management of migraine *Judith M Hockaday*

Personal view

1177 Selective medical examinations for school entrants: the way forward *S Richman, M Miles*

1182 **Sister journals—Europe** *G McClure*

1183 **Letters to the editor**

1186 **Autumn books**

1192 **Current research themes**

No 11 NOVEMBER 1990

Annotations

1193 Hearing screening in children—state of the art(s) *M P Haggard*
1196 The genetics of deafness *William Reardon, Marcus Pembrey*
1198 Postviral fatigue syndrome *B Lask, M J Dillon*

Original articles

1199 Endocrine function and morphological findings in disorders of the hypothalamo-pituitary area *Emanuele Cacciari, Stefano Zucchini, Gabriella Carla', et al*
1203 Increase in urinary growth hormone excretion in puberty *D A Price, G M Addison, E D Herbert*
1205 Assessment of gonadal maturation by evaluation of spermaturia *Franz Schaefer, Joachim Marr, Christoffer Seidel, et al*
1208 Indices of intact serum parathyroid hormone and renal excretion of calcium, phosphate, and magnesium *N J Shaw, J Wheeldon, J T Brocklebank*
1212 Helicobacter pylori and associated duodenal ulcer *C K Yeung, K H Fu, K Y Yuen, et al*
1217 Severe hypertension after liver transplantation in α_1 antitrypsin deficiency *G Noble-Jamieson, N D Barnes, S Thiru, et al*
1222 Corticosteroids in primary tuberculosis with bronchial obstruction *M Toppet, A Malfroot, M D Derde, et al*
1227 Virological investigations of acute encephalopathy in India *Rashmi Kumar, Asha Mathur, Arvind Kumar, et al*
1231 Perianal appearances associated with constipation *U Agnarsson, C Warde, G McCarthy, et al*
1235 Ventilator dependency in the United Kingdom *R O Robinson*
1237 Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus *Henriëtte A van Steensel-Moll, Jan A Hazelzet, Edwin van der Voort, et al*
1240 Effects of newborn screening of cystic fibrosis on reported maternal behaviour *Carol Boland, Norman L Thompson*
1245 Central nervous system vasculitis after chickenpox—cause or coincidence? *Avinoam Shuper, Eileen P G Vining, John M Freeman*
1249 Reproducibility of 24 hour oesophageal pH studies in infants *F J Hampton, U M MacFadyen, H Simpson*
1255 Bronchial asthma and acid reflux into the distal and proximal oesophagus *P M Gustafsson, N–I M Kjellman, L Tibbling*
1259 Air leaks and vasopressin release *N McIntosh, P Prakash, A Smith*
1263 Recognising failure to thrive in early childhood *A G K Edwards, P C Halse, J M Parkin, et al*
1266 Use of thermographic imaging to study babies sleeping at home *E S Anderson, M P Wailoo, S A Petersen*
1268 Continued need for pneumococcal prophylaxis after splenectomy *I A Murdoch, R Dos Anjos*
1269 Visceral leishmaniasis in a Scottish child *P Galea, K M Goel*

1270 Crohn's disease of the lung *J W L Puntis, M J Tarlow, F Raafat, et al*
1272 Topical anaesthesia for repair of minor lacerations *D H Bass, P J Wormald, J McNally, et al*
Commentary *D P Drake, P A Dale*
1274 Lymphocytes bearing the T cell receptor γ δ in human breast milk *A Bertotto, G Castellucci, G Fabietti, et al*
1275 Intravenous immunoglobulin in virus associated haemophagocytic syndrome *P Goulder, D Seward, C Hatton*

Regular review

1278 Helicobacter pylori *B Drumm*

Current topic

1283 The cytokines are coming *Kevin P Windebank*

Personal practice

1286 Head injury—how community paediatricians can help *Marion Crouchman*

1287 **Letters to the editor**

No 12 DECEMBER 1990

Editorial

1289 Duplicate publication and related problems

Annotations

1291 Surgery for gastro-oesophageal reflux *E M Kiely*
1293 Atrial natriuretic factor: the heart as an endocrine organ *T J Stephenson, F Broughton Pipkin*
1295 Cold comfort for the catarrhal child *David Isaacs*

Original articles

1297 Roseola infantum and other syndromes associated with acute HHV6 infection *W L Irving, J Chang, D R Raymond, et al*
1301 HIV-1 infection in a cohort of haemophilic patients *N Wagner, R Bialek, H Radinger, et al*
1305 Rectal temperature of normal babies the night after first diphtheria, pertussis, and tetanus immunisation *D Rawson, S A Petersen, M P Wailoo*
1308 Factors influencing the body temperature of 3–4 month old infants at home during the day *E S Anderson, S A Petersen, M P Wailoo*
1311 Abnormal small bowel permeability and duodenitis in recurrent abdominal pain *S B van der Meer, P P Forget, J W Arends*
1315 Growth velocity before sudden infant death *S M Williams, B J Taylor, R P K Ford, et al*
1319 Increasing asthma prevalence in a rural New Zealand adolescent population: 1975–89 *R A Shaw, J Crane, T V O'Donnell, et al*
1324 Long term outcome of ventilated asthmatics *P C Seddon, D P Heaf*
Commentary *Margaret A Branthwaite*
1329 Cerebral palsy: why we must plan for survival *P M Evans, S J W Evans, E Alberman*
1334 Human isophane or lente insulin? A double blind crossover trial in insulin dependent diabetes mellitus *D M Gibb, A B M Foot, B May, et al*
1338 Microbiological studies of the enterocolitis of Hirschsprung's disease *D Wilson-Storey, W G Scobie, K G McGenity*
1340 The reliability of height measurement (The Wessex Growth Study) *L D Voss, B J R Bailey, K Cumming, et al*
1345 Are measurements of height made by health visitors sufficiently accurate for routine screening of growth? *M L Ahmed, P L Yudkin, J A MacFarlane, et al*
1349 Psychological characteristics of children with Shwachman syndrome *A Kent, G H Murphy, P Milla*
1353 Increase in serum concentrations of IgG_2 and IgG_4 by selenium supplementation in children with Down's syndrome *G Annerén, C G M Magnusson, S L Nordvall*
1356 Late deaths after treatment for childhood cancer *M M Hawkins, J E Kingston, L M Kinnier Wilson*
1364 Diagnosis of Pneumocystis carinii pneumonia from non-invasive sampling of respiratory secretions *R A Hague, S E Burns, J Y Q Mok, et al*
1365 Cystic fibrosis, Pseudomonas aeruginosa, and selective decontamination *A Mark Dalzell, Hendrik K F van Saene, David P Heaf*
1367 Nocturnal faecal soiling and anal masturbation *A F Clark, P J Tayler, S R Bhate*

Current topic

1369 Retinal haemorrhages *Baljit Kaur, David Taylor*

Personal practice

1373 Development of a psychiatric liaison service *D Black, A McFadyen, G Broster*

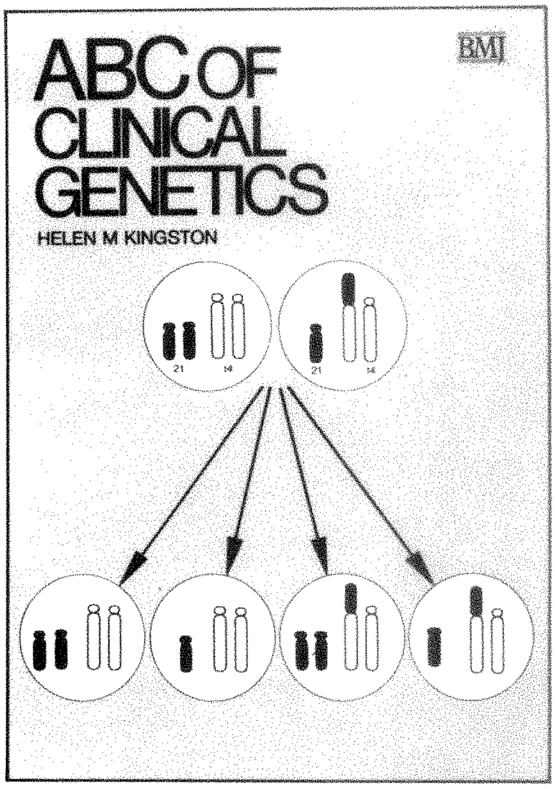
1376 **Referees and staff**

1378 **Letters to the editor**

1381 **Book reviews**

1385 **Index**

Genetics is a subject fundamental to medicine, but rapid advances in recent years may make the subject complex and confusing to clinicians and paramedical staff outside the specialty. Nevertheless, the demand for genetic investigation and counselling is increasing, and these services need to be offered by clinicians other than clinical geneticists. In the *ABC of Clinical Genetics* Helen Kingston, consultant clinical geneticist at St. Mary's Hospital, Manchester, reviews basic concepts of inheritance in mendelian, chromosomal, and multifactorial disorders; outlines the investigation and management of genetic conditions; and illustrates the application of recombinant DNA technology to clinical practice. Implications of genetic diseases for relatives are also considered, together with the ethical and human dilemmas that face doctors and patients and their families.



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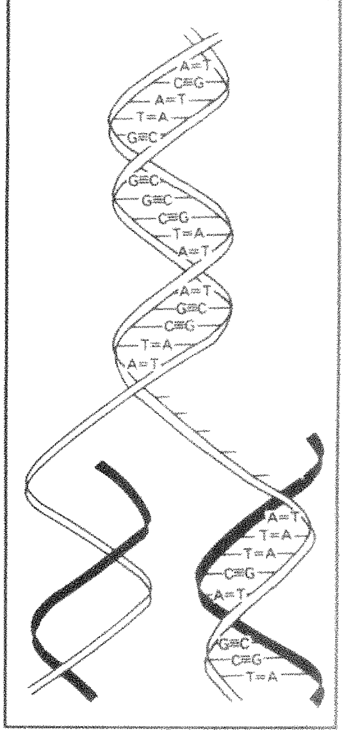

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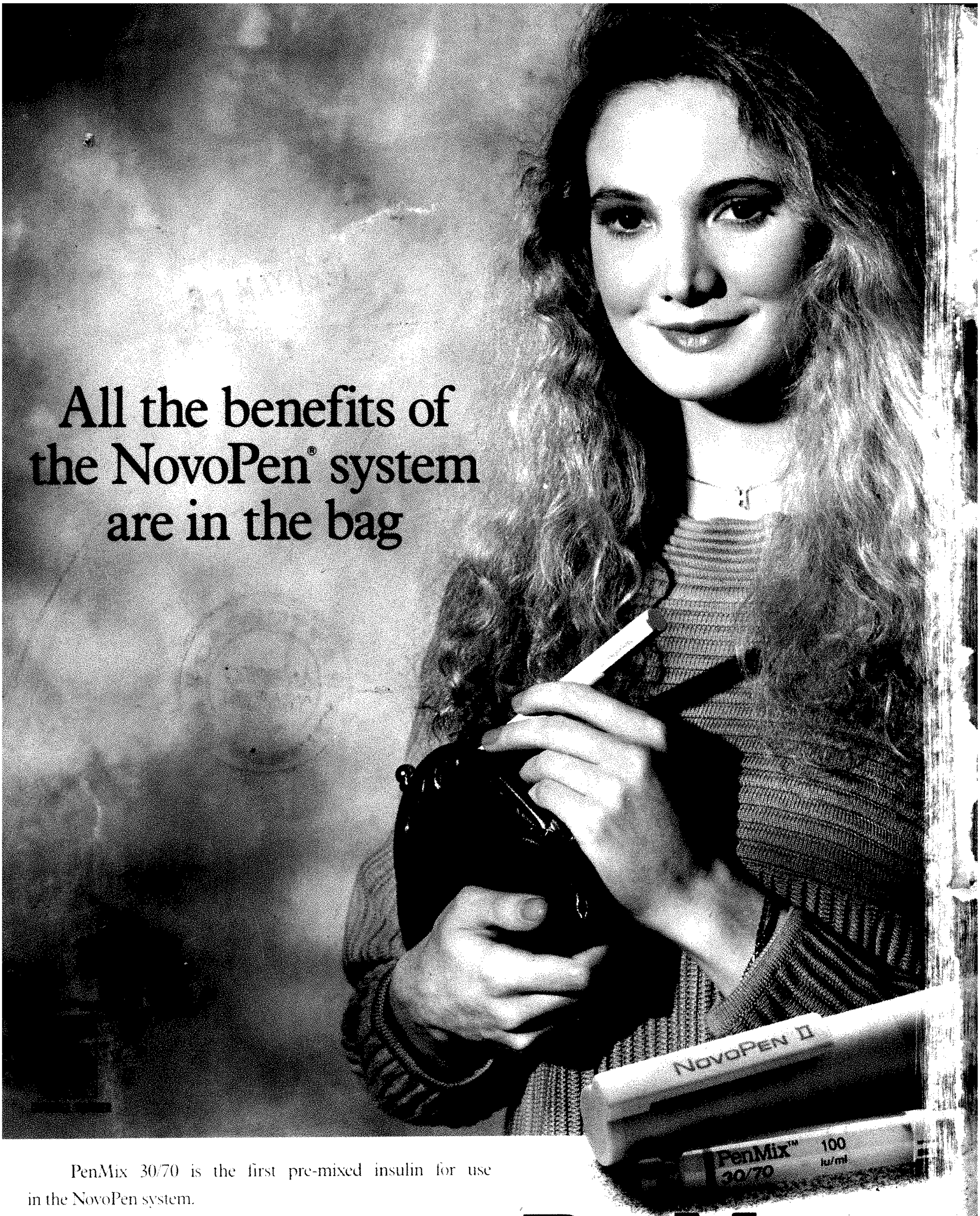
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